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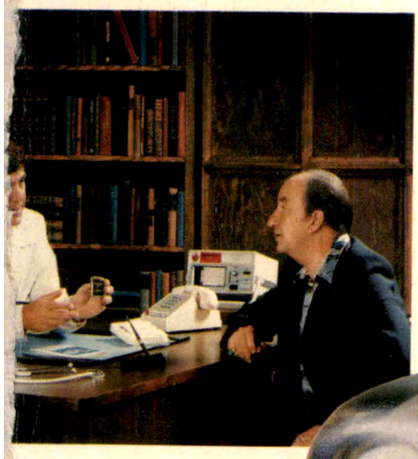

Intermedics introduces the Patient Lifetime Replacement Agreement on the InterLith™ model 223 pacemaker.

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A YORKE MEDICAL JOURNAL

Your confidence in Intermedics is as important to us as your patient's confidence is to you. That's why we want you to know about the InterLith™, chosen around the world as one of the most reliable pacemakers available.

Intermedics supports the outstanding reliability of the InterLith, and will allow a replacement on model 223 generators *which fail for any reason during the lifetime of the original user.

Extensive use has confirmed the outstanding performance and reliability of the InterLith. In addition to its proven reliability, the InterLith has significant features which make it an especially fine choice as a replacement pacemaker, one deserving of your confidence.

Confidence begins with extraordinary design features.

A tungsten inert gas (TIG) welding technique is used to hermetically seal the InterLith in a 316L stainless steel enclosure that prevents moisture leakage. A specially designed polycrystalline ceramic feedthrough seal, utilizing a 99.99% pure platinum conductor, makes the electrical connection to the pulse generator. The high collar design of the feedthrough minimizes fluid leakage in the harsh environment of the human body.

In addition, the InterLith is one of the smallest, lightest pacemakers on the market. Its corners are gently rounded, much as the contours of the patient's own body, minimizing the risk of pressure necrosis. The unipolar model weighs only 75 grams and measures 6.0 cm by 4.6 cm by 1.5 cm, enabling a smaller incision and a more cosmetic pocket for greatest patient comfort.

*The patient lifetime replacement agreement is limited to the standard model 223 pulse generator and does not include the 223-02 (High-Output) pulse generator. Consult the physician's handbook for these "special" pacemakers for their specific patient replacement agreements.

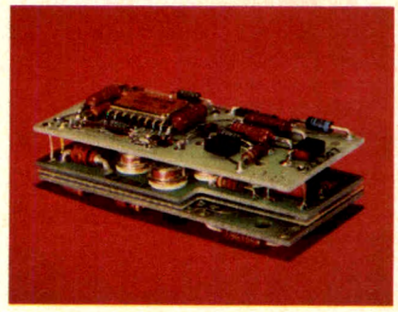
Confidence increases with superior performance.

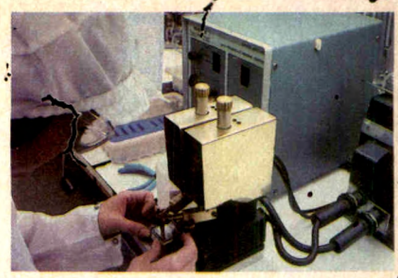
Sophisticated state-of-the-art technology in pacemaker electronics gives the InterLith an outstanding theoretical longevity in excess of 14 years. The InterLith's overall failure rate of less than 0.003 is attributable to the outstanding longevity of its lithium-iodide power cell, a battery without a single failure reported in 150,000 battery units manufactured. The power source, combined with the proven reliability of CMOS circuitry provides superior performance at the lowest possible power consumption.

Quality c[illegible]nsures confiden[illegible]

Every compo[illegible]nt utilized in the InterLith is selected and tested to meet the same standards as in the most exacting aerospace and military applications. Every step of the manufacturing process at Intermedics is subject to rigid quality assurance procedures in our complete environmental testing laboratory, because at Intermedics we believe only the highest quality products can merit your confidence. Some of the high reliability screening steps that our pacemakers receive in manufacturing are:

1. Twenty-four hour dynamic temperature cycling from −30° to +80° C.
2. Vibration testing at .1″ displacement and 10 g's from 20 HZ to 2 KHZ.
3. Strip chart rate recording from room temperature to 60°C.
4. Hermetic seal testing to 4×10^{-8} atm. cc/sec.





The InterLith has been designed and built to merit your confidence.

So, the next time one of your patients requires pacing therapy why not select the InterLith. Where reliability counts, there's no better choice.

Intermedics Inc.
P.O. Box 617
Freeport, Texas 77541

Our business is life.

INTERMEDICS PULSE GENERATORS

INDICATIONS FOR USE Implantable cardiac pulse generators may be indicated for long-term treatment of impulse formation and conduction disorders resulting in symptomatic bradyarrhythmias, tachyarrhythmias, and heart block unresponsive to drug therapy.

PRECAUTIONS Implanted pacemakers have a finite and relatively widely variable service life as a result of factors such as the initial capacity of the battery and the shelf storage time of the manufactured pacemaker; variations in electrode system resistances, stimulation rate, and the percentage of time the implanted pacemaker is inhibited; and random electronic component failures.

Pacemaker operation can be influenced by electric, magnetic, or electromagnetic energy mimicking normal cardiac activity. In addition, certain environmental sources can couple sufficient energy into a pacemaker system to damage the pulse generator. Specifically, diathermy should not be used on pacemaker patients because of possible total inhibition of the pulse generator; electrocautery can inhibit and/or damage the pacemaker as well as cause burns or possible ventricular fibrillation; defibrillation can damage the pacemaker, and the presence of the pacemaker may cause increased cardiac muscle damage from defibrillation. Certain electrical and gasoline-powered appliances can cause inhibition of an implanted cardiac pacemaker system.

For complete precautions, see the Physician's Manual for the Intermedics cardiac pulse generator to be used.

CONTRAINDICATIONS AND SIDE EFFECTS There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. Body rejection phenomena, local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

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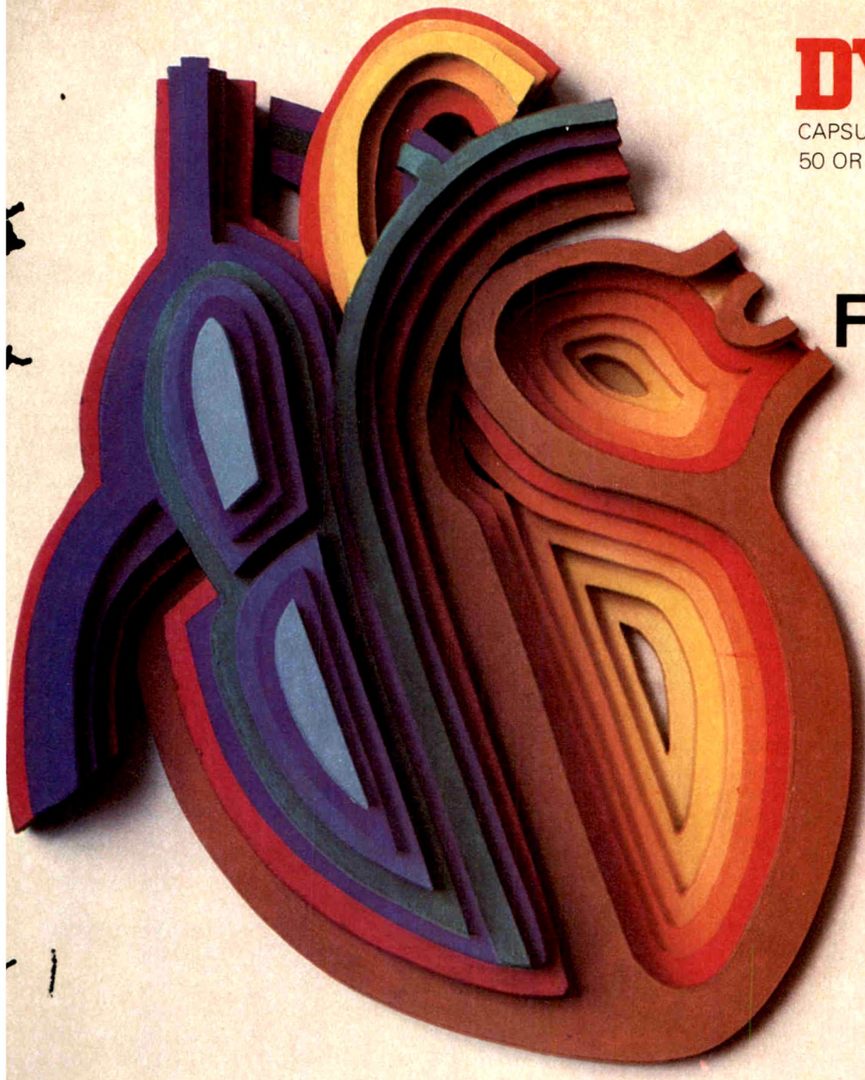

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When used with another diuretic, 'Dyrenium' has an additive effect; initial dosage of both agents should usually be reduced; careful supervision and dosage adjustment are required. K^+ supplements should be discontinued and not reinstituted unless hypokalemia develops or dietary K^+ intake is markedly reduced. K^+ supplements are contraindicated when 'Dyrenium' is used alone. Hyperkalemia can occur, but it is rare when renal function is normal. Serum K^+ and BUN should be checked regularly (see Warnings below).

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Indications: Edema associated with congestive heart failure, cirrhosis and nephrotic syndrome; steroid induced edema, idiopathic edema, and edema due to secondary hyperaldosteronism, to increase diuresis in patients resistant to other diuretics. Routine use of diuretics in healthy pregnant women is inappropriate; they are indicated in pregnancy when edema is due to pathological causes (see Warnings).

Contraindications: Anuria. Severe or progressive kidney disease or dysfunction. Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity. Continued use in developing hyperkalemia. Do not give potassium supplements, either by drug or by diet.

Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy requires weighing anticipated benefits against possible hazards to the fetus, including adverse reactions which have occurred in the adult. Triamterene may appear in breast milk. If its use is essential, the patient should stop nursing. 'Dyrenium' and spironolactone are not usually used concurrently; if they are, however, frequent serum potassium determinations are required.

Precautions: If hyperkalemia develops, withdraw the drug. The following may also occur: electrolyte imbalance, low-salt syndrome (with low salt intake), reversible mild nitrogen retention, decreasing alkali reserve with possible metabolic acidosis. Triamterene is a weak folic acid antagonist. Do periodic hematologic studies in cirrhotics with splenomegaly. Concomitant use with antihypertensive drugs may result in an additive hypotensive effect. When 'Dyrenium' is to be discontinued after intensive or prolonged therapy, withdraw gradually because of possible rebound kaliuresis.

Adverse Reactions: Diarrhea, nausea and vomiting (may indicate electrolyte imbalance), other gastrointestinal disturbances, weakness, headache, dry mouth, anaphylaxis, photosensitivity, elevated uric acid, rash.

Note: When combined with another diuretic, the initial dosage of each agent should be lower than recommended.

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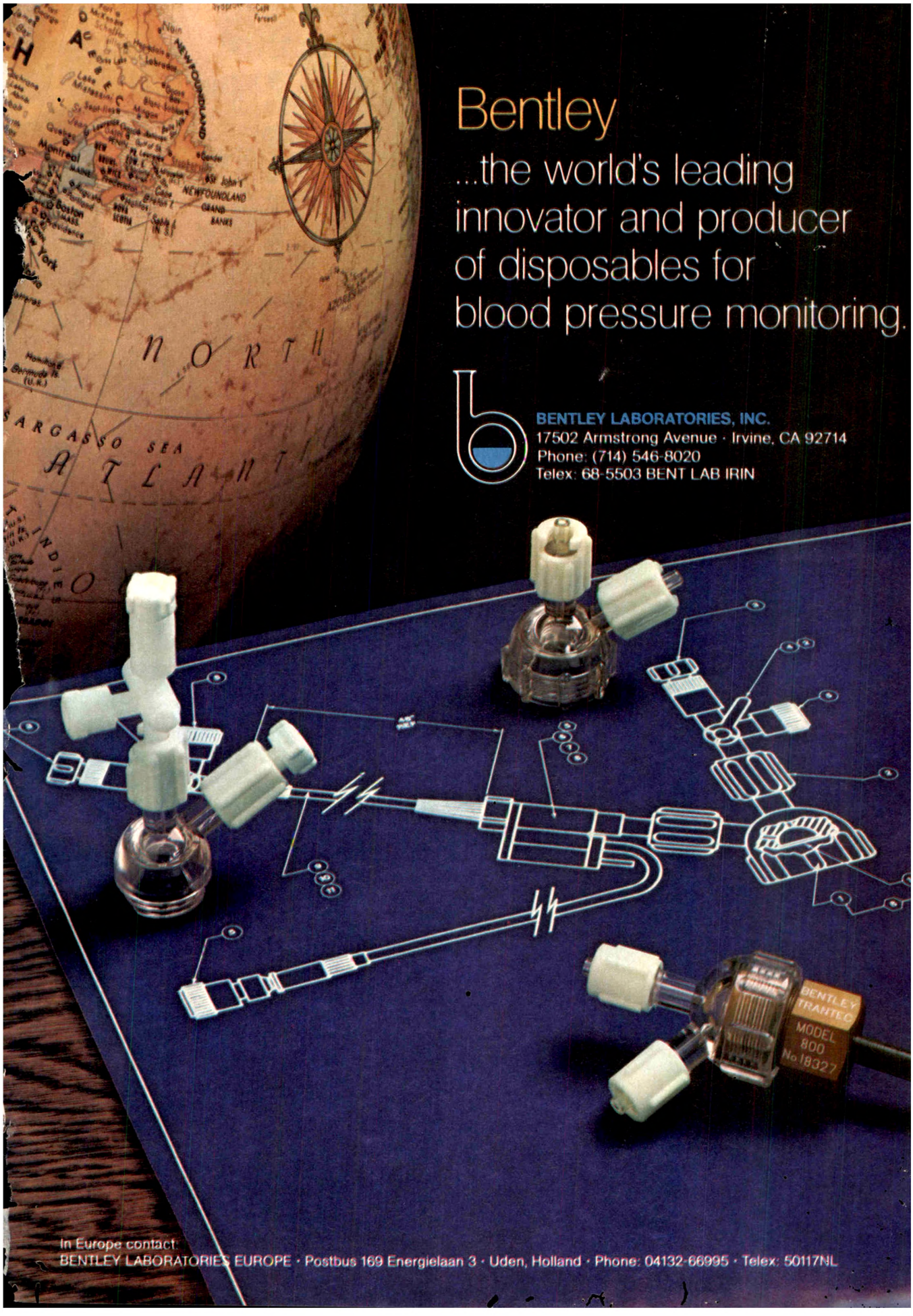
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Dynamic myocardial scintigraphy and electrocardiographic monitoring at rest and during submaximal exercise in 27 patients 2 to 3 weeks after acute myocardial infarction demonstrated that patients with an anterior infarct

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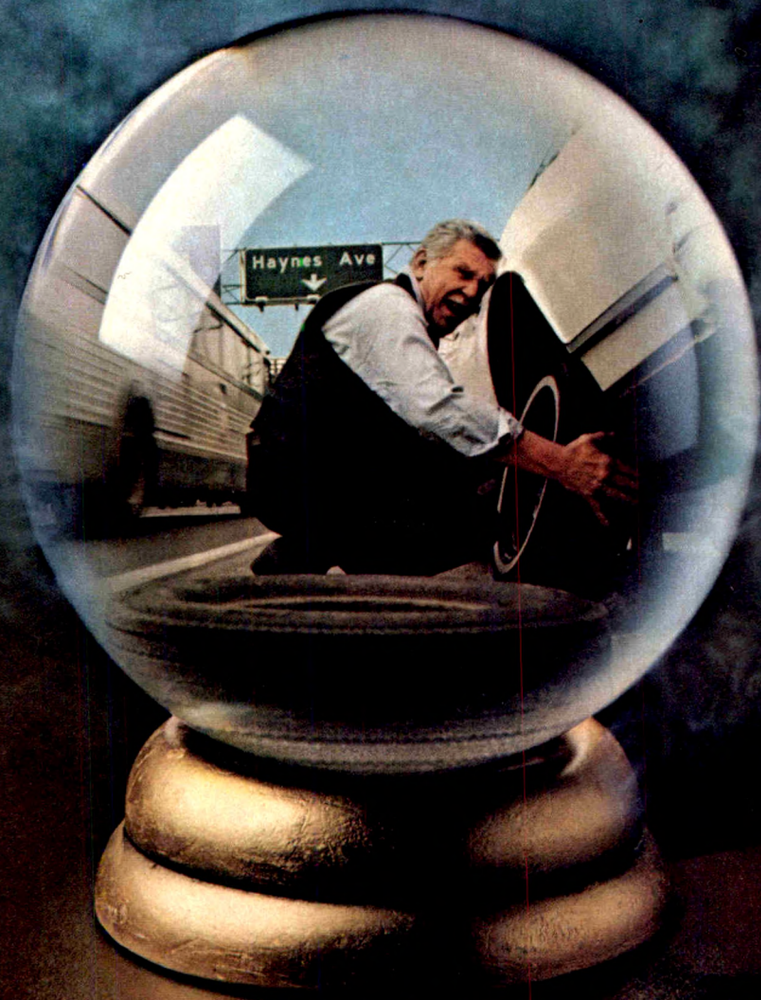
Predictable angina*



...during episodes of emotional stress or physical exertion

SUMMARY OF PRESCRIBING INFORMATION

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: The chewable dosage form of SORBITRATE is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.

Precautions: Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing, transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: *Individual Dose:* To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an angina attack. CHEWABLE SORBITRATE® (isosorbide dinitrate) may be taken for prompt relief of angina pain three or four times daily. Although the onset and duration of effect of coronary nitrates may vary, following is the generally reported range of these values for CHEWABLE SORBITRATE.

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Duration of Effect: One to two hours.

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have a different functional response to submaximal exercise at the time of hospital discharge than those with an inferior or nontransmural infarct. Those with a recent anterior myocardial infarct showed a significant reduction in left ventricular ejection fraction with submaximal exercise and segmental wall motion abnormalities at rest. The patients with an inferior or nontransmural infarct showed fewer and milder abnormalities at rest and after exercise. These exercise scintigraphic results appeared to be reproducible. Nine patients undergoing repeat submaximal exercise testing 6 weeks after discharge from the hospital had responses similar to those before discharge.

29 Comparison of S-T Segment Changes on Exercise Testing With Angiographic Findings in Patients With Prior Myocardial Infarction

MARK J. CASTELLANET, PAUL S. GREENBERG and MYRVIN H. ELLESTAD

Assessing the reliability of the exercise electrocardiogram in detecting additional coronary disease in 97 patients with prior transmural myocardial infarction, this study shows that the S-T response to the treadmill stress test had a high degree of sensitivity (87 percent) and specificity (90 percent) in patients with a previous anteroseptal wall infarction. A negative S-T response was of little value in distinguishing among groups of patients with single or multiple vessel coronary artery disease. A positive treadmill stress test does not necessarily imply multiple vessel disease. The resting surface electrocardiogram proved useful in predicting a false negative exercise test. Q waves in the precordial leads extending to lead V_4 or beyond decreased the sensitivity rate of treadmill stress testing to 33 percent.

36 Is the Treadmill Exercise Test Useful for Evaluating Coronary Artery Disease in Patients With Complete Left Bundle Branch Block?

FULVIO ORZAN, EFRAIN GARCIA, VIRENDRA S. MATHUR and ROBERT J. HALL

Clinical evaluation, treadmill exercise testing and cardiac catheterization data in 57 patients with complete left bundle branch block indicate that exercise-induced electrocardiographic changes do not facilitate detection of coronary artery disease in such patients. In this study the degree of S-T depression induced by exercise was not useful in detecting myocardial ischemia. Exertional chest pain was rarely accompanied by abnormal S-T changes. At present exercise-induced S-T changes in patients with left bundle branch block remain uninterpretable. In the future the utilization of radionuclide scanning techniques with thallium and similar agents during rest and exercise may prove useful in diagnosing myocardial ischemia in the presence of left bundle branch block.

41 Coronary Artery Disease in Young Women: Clinical and Angiographic Features and Correlation With Risk Factors

DAVID D. WATERS, CHRISTINE HALPHEN, PIERRE THEROUX, PAUL-ROBERT DAVID and HENRY F. MIZGALA

Contrary to some other evidence, this clinical and angiographic study of 239 women less than 45 years of age with suspected coronary artery disease showed that coronary artery disease in these young women did not differ in most respects from coronary disease in other patients. Hypertension, hyperlipidemia and diabetes were at least twice as frequent in women with significant coronary artery disease as in those with normal arteries. Cigarette smoking and a strong family history of coronary disease also correlated significantly with coronary artery disease. Diagnostic coronary arteriography is rarely necessary in women of this age group with less than two risk factors. In this series the prevalence of oral contraceptive use did not differ significantly between women with significant coronary disease and those with normal vessels. No characteristic type of coronary angiographic lesion was observed in users of oral contraceptive agents.

48 Nonobstructive Coronary Thrombosis in Sudden Cardiac Death

RICHARD J. FRINK, JAMES O. TROWBRIDGE and PIERCE A. ROONEY, Jr.

As shown in these six men aged 32 to 44 years without any history of heart disease, nonobstructing mural coronary thrombosis may be more prevalent and more significant than previously suspected in cases of sudden cardiac death. A nonobstructing mural coronary thrombus was found in all six hearts. In four, the thrombus was located in the left anterior descending coronary artery. Distal microthrombi were found in four hearts. The terminal event, often a ventricular arrhythmia, may have been related to the mural coronary thrombus. Small fragments originating from such lesions can obstruct the microcirculation, producing sudden lethal arrhythmias. The degree of thrombotic organization suggests that thrombi were present some time before death. All thrombi were superimposed on atherosclerotic lesions, but the thrombus was located at the site of greatest narrowing of the affected artery in only 50 percent of cases.

Continued on page A13

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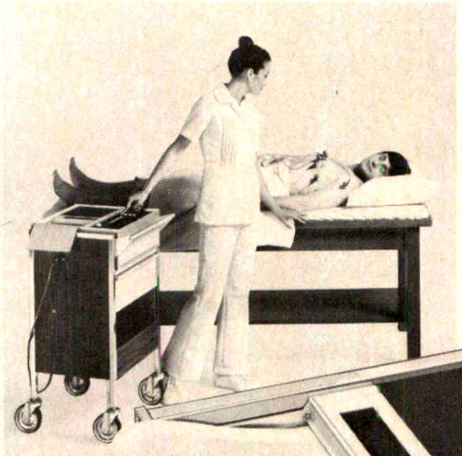

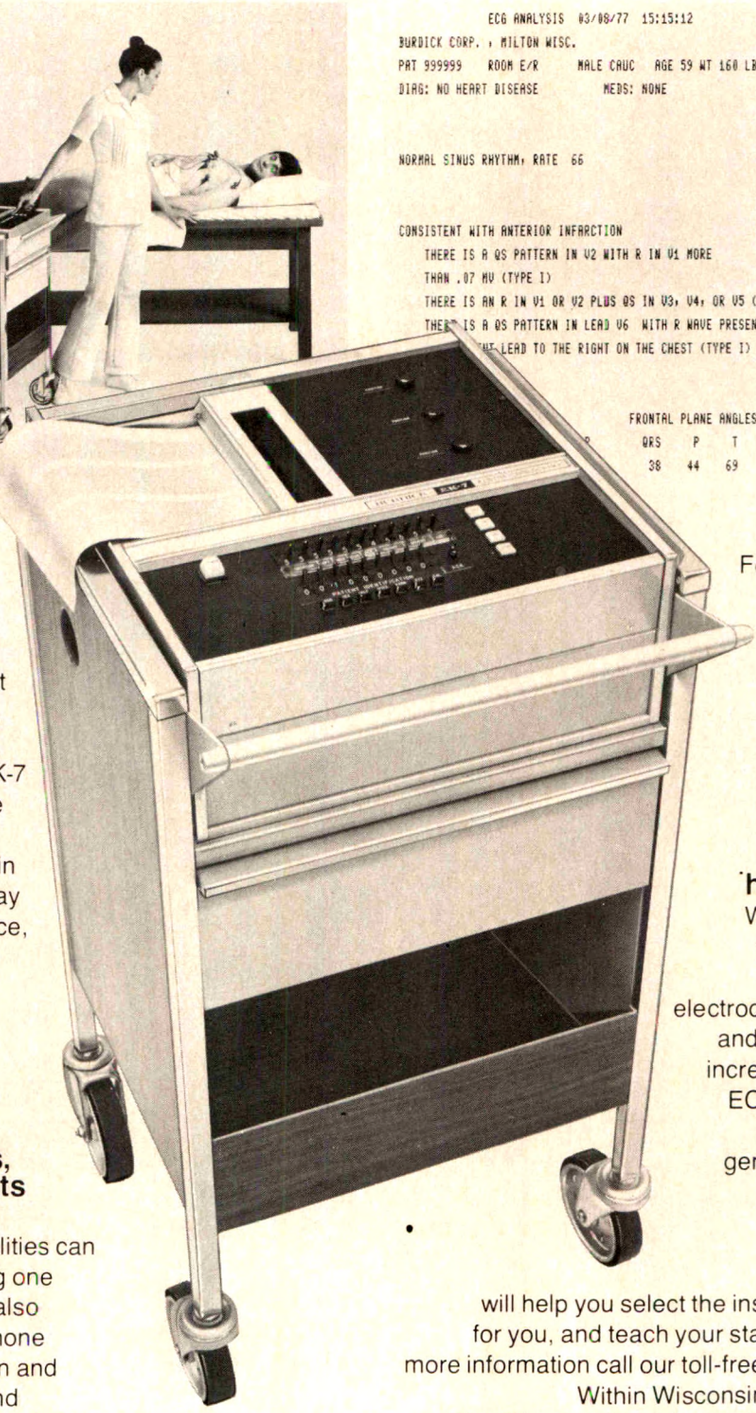

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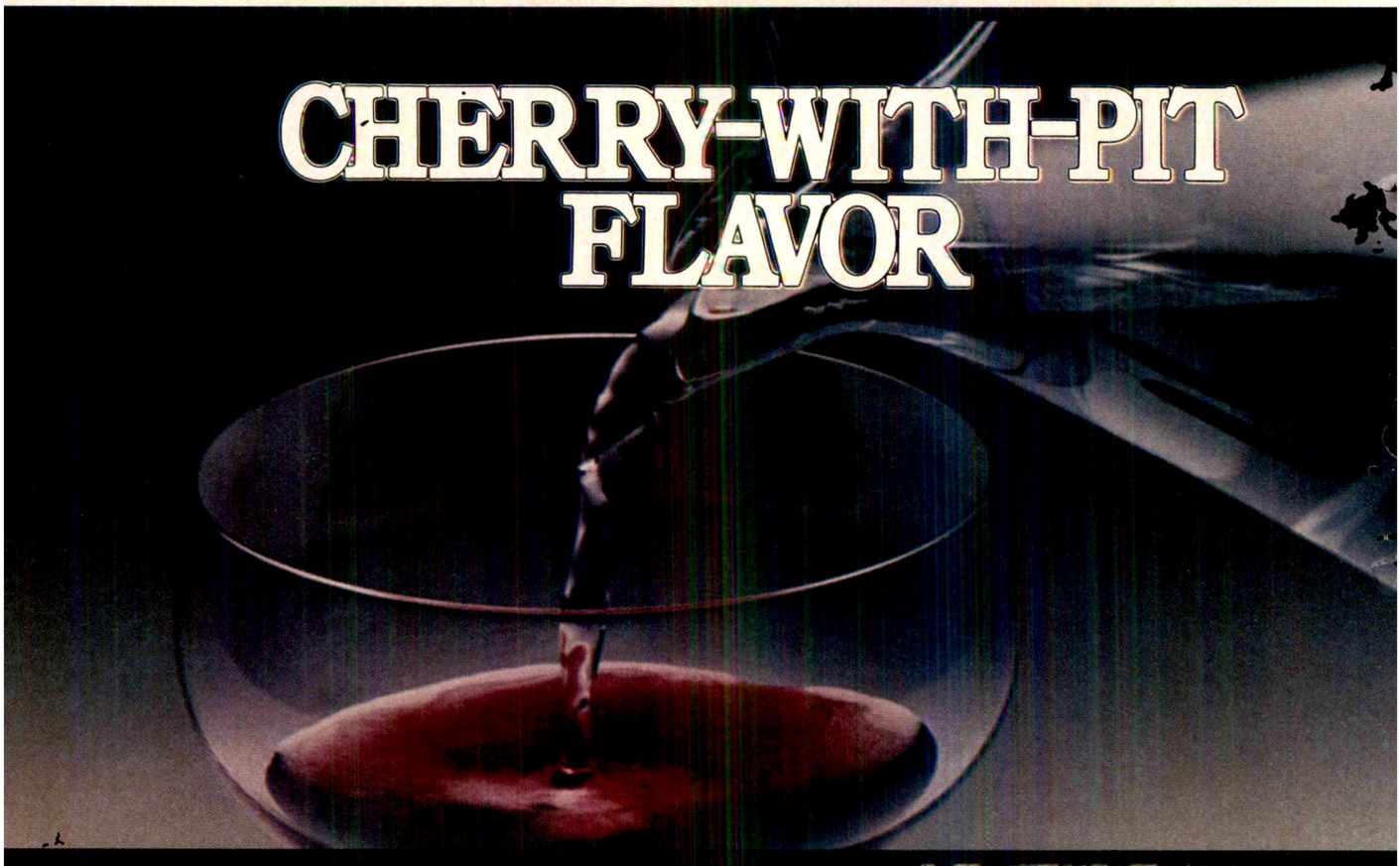

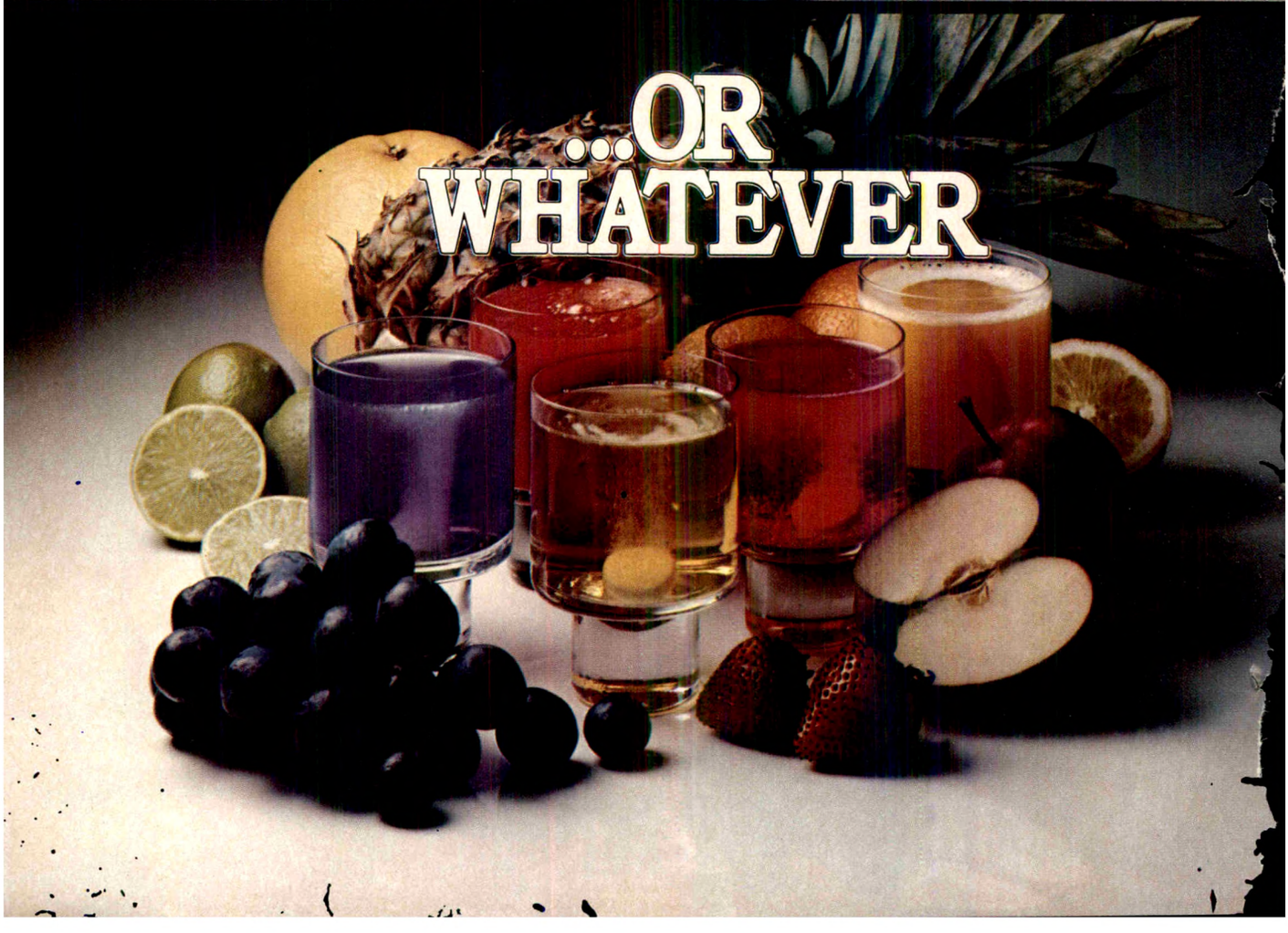

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Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

Indications: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

Contraindications: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements.

Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis.

High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest.

To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve each Klorvess Effervescent Tablet in 3 to 4 ounces of water or fruit juice, or dilute each tablespoonful of Klorvess (potassium chloride) 10% Liquid in 3 to 4 ounces of water. Both of these solutions should be ingested slowly with or immediately after meals.

Adverse Reactions: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts.

The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest.

The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

Dosage and Administration: Klorvess Effervescent Tablets: Adults—One Klorvess Effervescent Tablet (20 mEq each of potassium and chloride) completely dissolved in 3 to 4 ounces of cold water or fruit juice 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) of Klorvess Liquid (20 mEq of potassium chloride) completely diluted in 3 to 4 ounces of water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating. Deviations from these recommended dosages may be indicated in certain cases of hypokalemia based upon the patient's status. The average total daily dosage must be governed by the patient's response as determined by frequent evaluation of serum electrolytes, EKG and clinical status.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

Treatment of Hyperkalemia: 1. Dextrose solution, 10 or 25% containing 10 units of crystalline insulin per 20 g dextrose, given IV in a dose of 300 to 500 ml in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resins, orally and as retention enema. (Caution: Ammonium compounds should not be used in patients with hepatic cirrhosis.) 3. Hemodialysis and peritoneal dialysis. 4. The use of potassium-containing foods or medicaments must be eliminated. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

How Supplied: Klorvess Effervescent Tablets (white)—60 tablets (2 Rx units of 30 effervescent tablets each). Each tablet is individually foil wrapped. Klorvess (potassium chloride) 10% Liquid (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Tablets and Liquid are also available in institutional packaging as follows: Klorvess Tablets—30 and 1000 tablets; Klorvess Liquid—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

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*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.
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CONTENTS

52 Rapid Changes in Left Ventricular Dimensions and Mass in Response to Physical Conditioning and Deconditioning

ALI A. EHSANI, JAMES M. HAGBERG and ROBERT C. HICKSON

These results indicate that adaptive changes in left ventricular dimension and wall thickness occur rapidly in response to endurance training and regress rapidly after cessation of training. Left ventricular end-diastolic dimension in eight competitive swimmers increased from the pretraining value of 48.7 ± 1.7 to 53 ± 0.2 mm by the first week and to 52 ± 1.7 mm by the ninth week of training, mimicking the pattern of chronic volume overload. Maximal oxygen uptake (VO_2 max) increased from 52 ± 3 to 60 ± 3 ml/kg per min. In the six competitive runners who stopped training for 3 weeks, left ventricular end-diastolic dimension decreased progressively from the control value of 51 ± 3 to 46.3 ± 2.3 mm; posterior wall thickness decreased from 10.7 ± 0.3 to 8.0 ± 0.7 mm and VO_2 max from 62 ± 2 to 57 ± 2 ml/kg per min. Despite the reduction in end-diastolic volume, changes in ejection fraction were negligible, suggesting that mechanical performance of the left ventricle may not be affected significantly by deconditioning.

57 Association of Left Dominant Coronary Arterial System With Congenital Bicuspid Aortic Valve

GROVER M. HUTCHINS, IRADJ H. NAZARIAN and BERNADINE H. BULKLEY

This review of postmortem arteriograms by patterns of coronary arterial dominance and examination of the hearts for aortic valve disease in 973 autopsy patients confirms the association of left coronary arterial dominance with congenital bicuspid aortic valve. These vessels suggest that a left dominant coronary system may be the consequence of disproportionately decreased blood flow in the left heart chambers. Aortic valve stenosis during early cardiogenesis may be one such cause.

60 Mitral Ring Calcification in Idiopathic Hypertrophic Subaortic Stenosis

ITZHAK KRONZON and EPHRAIM GLASSMAN

In this study of 68 patients with idiopathic hypertrophic subaortic stenosis, the prevalence of mitral anular calcification was greater than in age-matched control subjects without idiopathic hypertrophic subaortic stenosis. Calcification of the mitral valve anulus is a frequent finding in older patients with idiopathic hypertrophic subaortic stenosis, and its demonstration should raise the suspicion of associated idiopathic hypertrophic subaortic stenosis. Mitral anular calcification can be recognized on echocardiography by a dense thick linear echo behind the mitral valve that disappears abruptly at the junction between the left ventricle and the left atrium. Prolonged murmurs in patients with mitral anular calcification were thought to be caused by mitral regurgitation or aortic stenosis, but this study suggests that asymmetric septal hypertrophy or idiopathic hypertrophic subaortic stenosis may be a causative factor in some of these patients. Echocardiography may permit a more accurate diagnosis in such cases.

EXPERIMENTAL STUDIES

67 Radioautographic Studies in Experimental Myocardial Infarction: Profiles of Ischemic Blood Flow and Quantification of Infarct Size in Relation to Magnitude of Ischemic Zone

PANTEL S. VOKONAS, PAUL M. MALSKY, SHARI J. PAUL, STANLEY L. ROBBINS and WILLIAM B. HOOD Jr.

In dogs with myocardial infarction produced experimentally by ligation of a branch of the left circumflex artery, photodensitometric scanning of radioautograms was performed. The procedure revealed symmetric profiles of decreasing blood flow from each normal margin to the center of the infarct in the transverse plane and an asymmetric profile of decreasing blood flow from the epicardium to the center of the infarct and a subsequent increase near the endocardial surface in the transmural plane. Comparative analysis of radioautograms with corresponding adjacent histologic sections showed that myocardial necrosis was first evident at an average blood flow reduction of 45.2 ± 3.2 percent of normal values. A border zone of intermediate flow reduction that averaged 4.5 ± 0.5 mm and encompassed 30.4 ± 3.0 percent of total ischemic zone width was observed 24 hours after infarction. The size of the myocardial infarct in these experiments was approximately 40 percent of that of the ischemic zone. Determination of blood flow derived exclusively from collateral vessels was not possible with this technique.

Continued on page A17

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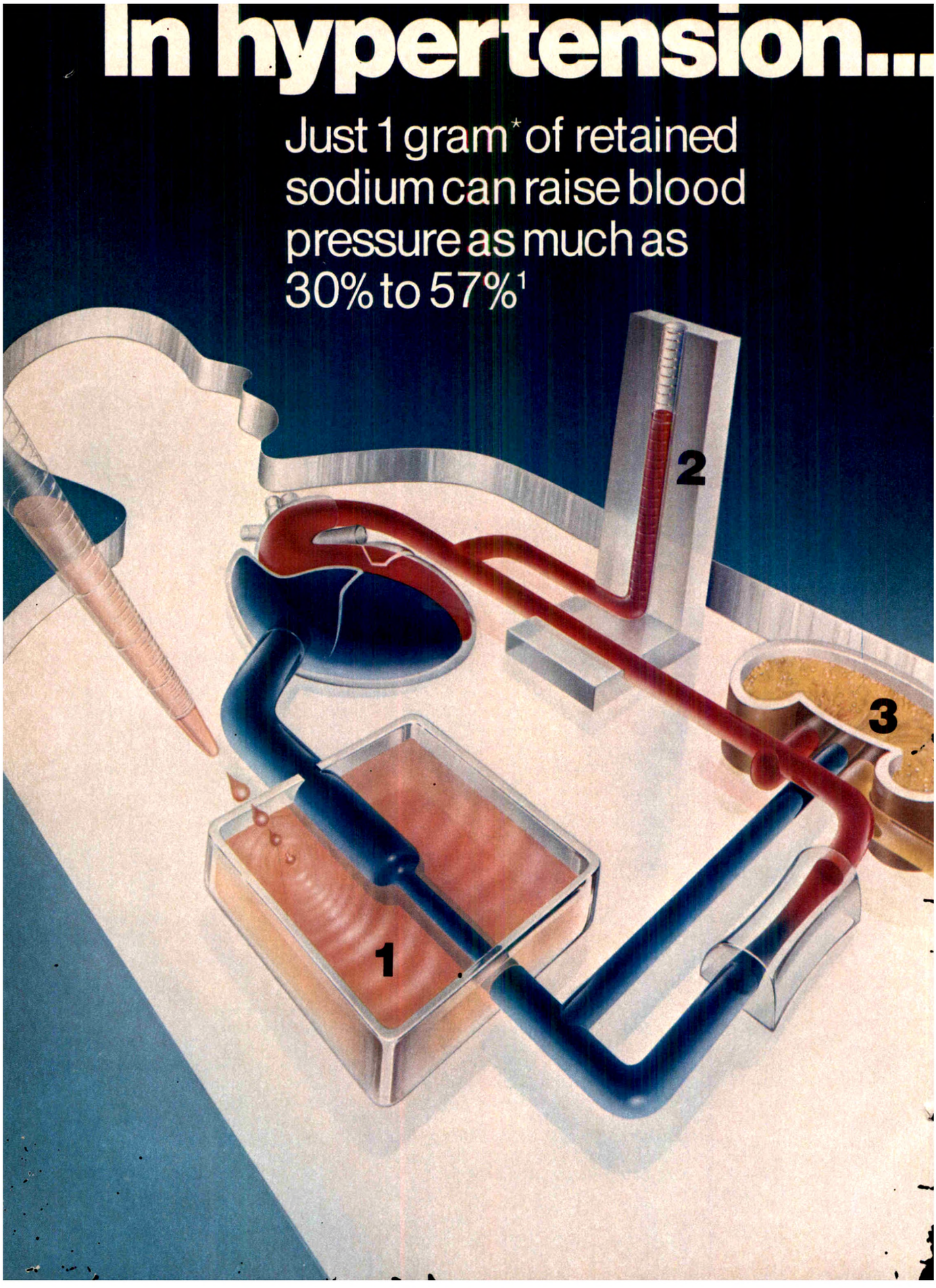

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*All values given in this example are approximations based on standard physiologic data and solute-volume relationships.

†From a baseline of 80 mm. Hg diastolic.

BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema.

Contraindications: Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.

Warnings: Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.

Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

Adverse Reactions: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

Usual Dose: One tablet daily.

How Supplied: Tablets—100 mg. (white, scored) and 50 mg. (aqua) in bottles of 100 and 1000; PAKs of 28 tablets, boxes of 6: unit-dose blister packs, boxes of 100 (10 x 10 strips).

References:

1. Guyton, A.C.: Regulation of arterial pressure: II. The renal-body fluid system for long-term pressure control. Mechanisms of hypertension, in Textbook of Medical Physiology, Philadelphia, Saunders, 1976, p. 281. **2.** Kaplan, N.: Treating hypertension: The results are in, in Mandates Hypertension (Kaplan, N.M., ed.), New York, Medcom, 1976, p. 6. **3.** Finnerty, F.A., Jr.: Hypertension: The Continuing Challenge, Scientific Exhibit, Meeting of AAFP, Boston, Mass., Sept. 20-23, 1976. **4.** Fries, E.D.: The treatment of hypertension: Why, when and how, in Hypertension Manual (Laragh, J.H., ed.), New York, Dun-Donnelley, 1974, p. 751. **5.** Tarazi, R.C.: Modern concepts in diuretic therapy, Postgrad. Med. 56:37, 1974.

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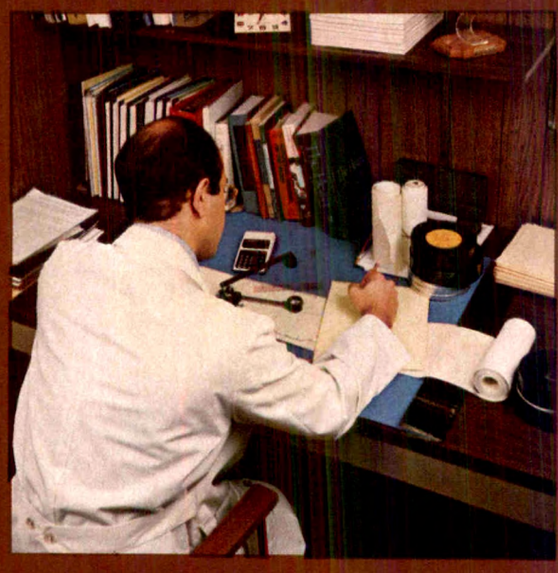

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CONTENTS

76 Effects of Tocainide on Ventricular Fibrillation Threshold

INGELA SCHNITTGER, JERRY C. GRIFFIN, ROGER J. HALL, PETER J. MEFFIN and ROGER A. WINKLE. *With the technical assistance of* FLORA PETERS and ROBERT KERNOFF

In this dog experiment, tocainide, a primary amine analog of lidocaine, significantly increased the right ventricular fibrillation threshold, but this increase was less than that observed at clinically tolerated lidocaine plasma concentrations. These animal data suggest that there may be advantages in continuing drug administration beyond the point when ventricular ectopic complexes are suppressed or minimal, or average "therapeutic" plasma concentrations are achieved. They also support the clinical concept that greater lidocaine concentrations are more protective against ventricular fibrillation.

82 Left Ventricular Function in Exercise-Induced Hypertrophy in Dogs

THOMAS E. CAREW and JAMES W. COVELL

Results in this study of left ventricular function and diastolic compliance in 10 average exercise-trained greyhounds with left ventricular hypertrophy suggest that neither isovolumic phase nor ejection phase indexes of contractility are altered in the hypertrophic heart of the greyhound under resting conditions. Under the stress of volume load of dextran, the hypertrophic greyhound heart showed essentially the same response with regard to ejection phase and isovolumic phase contractility indexes as the hearts of normal dogs. With volume load there was no significant change in mean velocity of circumferential fiber shortening in either group, but maximal first derivative of left ventricular pressure (dP/dt) increased about 10 percent in both groups. The pronounced increase in heart rate of 75 percent above resting levels seen during volume loading was perhaps the most striking hemodynamic indication of the effects of race conditioning in the greyhounds. This study supports the view that "physiologic hypertrophy" represents a useful adaptation to repetitive strenuous exercise. Exercise-induced hypertrophy, as found in these greyhounds, represents a physiologic adaptation and can be considered a variant of normal.

METHODS

89 Problems in Ultrasonic Estimates of Septal Thickness

JOHN W. ALLEN, SUN JUNE KIM, W. ALLAN EDMISTON and K. VENKATARAMAN

These data from studies in a cadaver model and 13 patients indicate that both endocardial misidentification and anatomic variation in septal thickness should be considered in reporting septal thickness measurements, especially when echocardiographic findings do not coincide with other clinical data. In this study, echographic contrast agents delineate an endocardial echo in the central portion of the ultrasonic beam. A specular (mirror-like) reflector exists within the right ventricular cavity and specular reflection within the septum may give a false impression of border-forming echoes. Spurious echoes, relating to a wide beam angle, can be confused with the endocardial echo. With use of the notch in the left septal echo, the specular quality of the right septal echo and the association of multiple myocardial echoes moving in parallel as criteria for endocardial echographic identification, the endocardial echoes in 11 of the 13 patients could be accurately identified without the use of a contrast agent.

PEDIATRIC CARDIOLOGY

97 Cerebrovascular Abnormalities in Postoperative Coarctation of Aorta

MICHAEL G. SAALOUKE, LOWELL W. PERRY, DAVID L. BRECKBILL, STEPHEN R. SHAPIRO and LEWIS P. SCOTT III

As shown in this study of 15 children, patients with central nervous system symptoms and a disparity of blood pressure in the arms after surgery for coarctation of the aorta should be carefully evaluated to exclude subclavian steal as the cause of their symptoms. In this group, four children manifesting central nervous system symptoms postoperatively and greater blood pressure in the right arm than in the left showed evidence of subclavian steal, with retrograde filling of the left ventricle and left subclavian arteries on selective right vertebral arteriography. Ligation of the left vertebral artery in three patients and left subclavian graft arterioplasty in one patient eliminated the neurologic symptoms, including persistent headaches, exercise-induced hemianopsia and major motor seizures. Surgery is not recommended for the asymptomatic patient. Spontaneous recovery as a result of development of adequate collateral vessels can occur in many patients.

Continued on page A19

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CONTENTS

102 Congenital Aortic Stenosis Secondary to Dysplasia of Congenital Bicuspid Aortic Valves Without Commissural Fusion

MELVIN D. CHEITLIN, JOHN J. FENOGLIO, HUGH A. McALLISTER, Jr., JAMES E. DAVIA and CARLOS M. DeCASTRO

In the hearts of nine children with clinical evidence of congenital valve stenosis and a congenital aortic valve, the two commissures of the valve were free to the aortic cusp. The cusps were thickened, rolled and redundant. On microscopic examination they consisted of loose connective tissue consistent with a dysplastic or incompletely differentiated valve. The valve orifice was obstructed by the dysplastic cusps, and dysplastic changes rather than the commissural fusion were responsible for the observed aortic stenosis. Clinically, especially at the time of surgery, it is important to distinguish the dysplastic bicuspid or tricuspid aortic valve with normal commissures from the unicommissural or acommissural aortic valve. Severe aortic stenosis in patients with a dysplastic bicuspid aortic valve, as in these children, is secondary to the thickened redundant aortic cusps rather than to commissural fusion or absence of commissures. Valvotomy probably offers little relief in these patients.

108 Echocardiographic Features of Total Anomalous Pulmonary Venous Drainage Into the Coronary Sinus

KALIM U. AZIZ, MILTON H. PAUL, SAROJA BHARATI, MAURICE LEV and KATHLEEN SHANNON

Echocardiograms in five infants with total anomalous pulmonary venous drainage into the coronary sinus and in one child with a secundum atrial septal defect and a large coronary sinus demonstrate that an enlarged coronary sinus is positioned constantly posterior to the left atrium in approximately the same horizontal plane as the aortic valve. Echocardiogaphically, the coronary sinus can be located as an echo complex behind the left atrium by using the aortic root as a reference point. The additional demonstration of the enlarged common pulmonary venous chamber behind the right atrium confirms the diagnosis of anomalous pulmonary venous drainage to the coronary sinus.

EPIDEMIOLOGY

114 Death From Ischemic Heart Disease in Young Finns Aged 15 to 24 Years

KIMMO KOSKENVUO, MARTTI J. KARVONEN and VILJO RISSANEN

Ischemic heart disease was diagnosed as the cause of death in 34 young Finns who died at age 15 to 24 years. Autopsy in 19 cases showed a stenosing process in the coronary arteries of 17 patients. Among 15 to 19 year olds the stenosis was generally ostial and nonsclerotic; ostial stenosis was found in half of this group. After age 20 atherosclerosis was the major cause of coronary stenosis. There appear to be few opportunities to predict sudden death from ischemic heart disease among the young. Sudden death often occurs during or immediately after physical exertion. Three of the four subjects with ostial stenosis had a history of symptoms, arrhythmias or chest pain. These results suggest that in men under age 20 years, death from ischemic heart disease arising from stenosing coronary atherosclerosis is rare, but by age 25 the natural course of coronary atherosclerosis begins to take its first victims.

119 Remission of Clinical Angina Pectoris: the Framingham Study

WILLIAM B. KANNEL and PAUL D. SORLIE

In this group of 74 men and 84 women with newly acquired angina uncomplicated by other manifestations of coronary heart disease, remission of new angina for at least 2 years occurred in 32 percent of the men and 44 percent of the women. In angina that had persisted for several years, the subsequent remission rates were lower. Persistence of symptoms indicates a more severe form of the disease characterized by nonspecific S-T segment or T wave abnormalities and a greater incidence of myocardial infarction and death than in subjects with transient angina. These results indicate a need for more detailed routine studies to exclude other possible causes of chest pain in such subjects with remittent angina. The mechanism responsible for the disappearance of angina is not well established. Such disappearance of angina is probably more often the result of a decrease in demand on the heart as the patient learns to live within his exercise tolerance than of the development of collateral circulation to compensate for the compromised circulation to the ischemic segment of myocardium.

Continued on page A21

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REPORTS ON THERAPY

124 Disease of the Left Main Coronary Artery. Surgical Treatment and Long-Term Follow-Up in 267 Patients

JOSE B. FARINHA, MARVIN A. KAPLAN, CLIFFORD N. HARRIS, EDWARD F. DUNNE, RONALD A. CARLISH, JEROME HAROLD KAY and SAMUEL BROOKS

Saphenous vein bypass graft surgery was performed with an operative mortality rate of 7 percent in 267 patients with left main coronary arterial narrowing. In these patients there was a 92.2 percent survival rate at 1 year, and a rate of 91, 89 and 86 percent at 2, 3, and 4 3/4 years, respectively. Seventy-five percent of patients were angina-free, and 22.4 percent had less angina. Of 128 grafts in 51 patients, 85 percent remained patent. These results indicate improved survival and reduced symptoms after saphenous vein bypass graft surgery in patients with left main coronary arterial narrowing. In patients with left main coronary artery disease, angiographic evaluation is within acceptable risk limits, and coronary bypass grafting is the treatment of choice.

129 Pharmacokinetics and Bioavailability of Digoxin Capsules, Solution and Tablets After Single and Multiple Doses

BRIAN L. LLOYD, DAVID J. GREENBLATT, MARCIA D. ALLEN, JEROLD S. HARMATZ and THOMAS W. SMITH

As shown in 12 healthy male volunteers, the bioavailability of digoxin capsules is equivalent to that of a solution and significantly greater than that of a reference tablet formulation. Using a slow intravenous infusion as the reference standard for 100 percent systemic availability, the investigators found that the systemic availability of the capsule preparation was significantly less than 100 percent. No striking or consistent difference was found among oral preparations in within- or between-subject coefficients of variation of systemic availability after ingestion of either single or multiple doses. Peak plasma digoxin levels after ingestion of the various oral preparations tended to be highest with the digoxin capsules.

CASE REPORTS

137 Three Cases of Hypotension and Syncope With Ventricular Pacing: Possible Role of Atrial Reflexes

CARLO ALICANDRI, FETNAT M. FOUAD, ROBERT C. TARAZI, LON CASTLE and VICTOR MORANT

As shown in three patients, syncope or severe lightheadedness, or both, can occur despite adequate ventricular pacing as a result of lower arterial pressure related to loss of effective atrial contraction and failure of the normal compensatory response of peripheral resistance rather than to changes in cardiac output alone. Hemodynamic studies in three patients during effective ventricular pacing demonstrated a decrease in cardiac output ranging from almost no decrease to 15 percent. The coincidence of a decrease in arterial pressure during atrioventricular dissociation with the recording of cannon waves in atrial tracings suggests that the paradoxic behavior of peripheral resistance may be related to an atrial reflex. When the atrium contracts against a closed valve, a momentary vasodilating reflex can be induced by stimulation of some atrial *A* vagal receptors. Arterial pressure during atrioventricular dissociation thus appears to be balanced by two opposite reflexes: the baroceptor reflex, which attempts to compensate for reduction in output, and atrial distension, which reduces peripheral resistance.

143 Cardiac Sarcoidosis. Diagnosis With Endomyocardial Biopsy and Treatment With Corticosteroids

BEVERLY LORELL, EDWIN L. ALDERMAN and JAY W. MASON

This interesting case of a 27 year old black housewife hospitalized for progressive dyspnea, fatigue and retrosternal chest pain illustrates the problem of diagnosing cardiac sarcoidosis in the absence of other organ involvement. The use of percutaneous transvenous endomyocardial biopsy permitted the diagnosis of cardiac sarcoidosis and the initiation of corticosteroid therapy. With steroid therapy the patient's dyspnea and radiographic and echographic measures of ventricular performance improved. It is important to suspect cardiac sarcoidosis in young adults with cardiomyopathy, conduction disturbances or other electrocardiographic abnormalities. In such cases in which cardiac sarcoidosis is strongly suspected, multiple endomyocardial biopsy specimens may increase the diagnostic specificity of the procedure.

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147 **Lack of Connection Between the Atria and the Peripheral Conduction System in a Case of Corrected Transposition With Congenital Atrioventricular Block**

SAROJA BHARATI, CAROLYN M. McCUE, JON B. TINGELSTAD, MICHAEL MANTAKAS, FERGUS SHIEL and MAURICE LEV

This infant, the first of premature twins born to a 33 year old white woman, died 2 weeks after birth and was found at autopsy to have corrected transposition of the great vessels and congenital atrioventricular (A-V) block with no connection between the atria and an anterior type of conduction system. Fibrosis and calcification replaced the absent atrial musculature. The pathogenesis of this lesion is unknown but may possibly be related to connective tissue dysplasia in the mother who had positive rheumatoid factor but who was asymptomatic. Despite poor contractility of the ventricle, mild mitral regurgitation and a patent foramen ovale, the second twin continues to thrive at age 2 years.

EDITORIALS

154 **Coronary Bypass Surgery Weighed in the Balance**

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163 **American College of Cardiology News**

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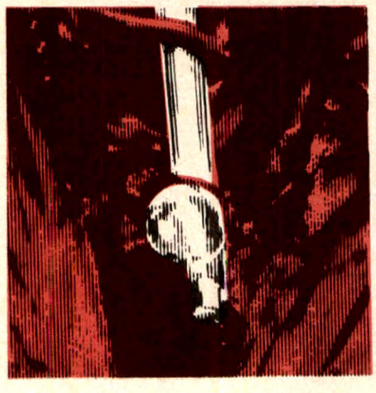

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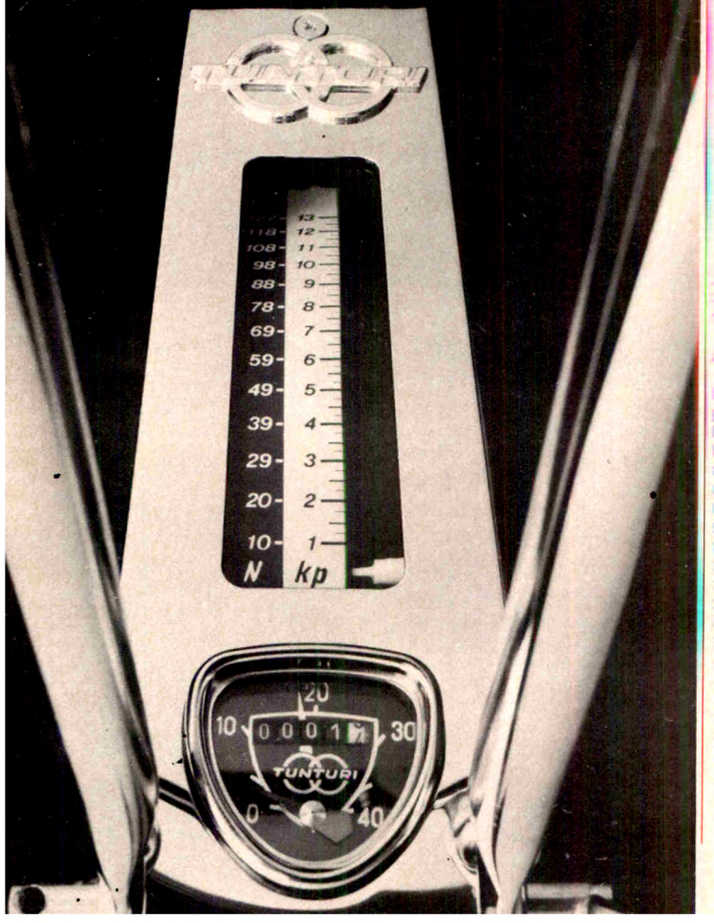

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ADMINISTRATION: Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

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Bear in mind when treating ventricular arrhythmias in patients with severe organic heart disease and ventricular tachycardia that complete heart block, which may be difficult to diagnose, may be present. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

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A syndrome resembling lupus erythematosus has been reported (see Precautions). Reactions consisting of fever and chills have been reported, including a case with nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy; and the patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever or any symptoms of upper respiratory tract infection. If any of these symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, and hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported.

The package insert should be read carefully to become familiar with the recommended dosage for the indicated conditions and for full prescribing information.

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See preceding page for brief summary.

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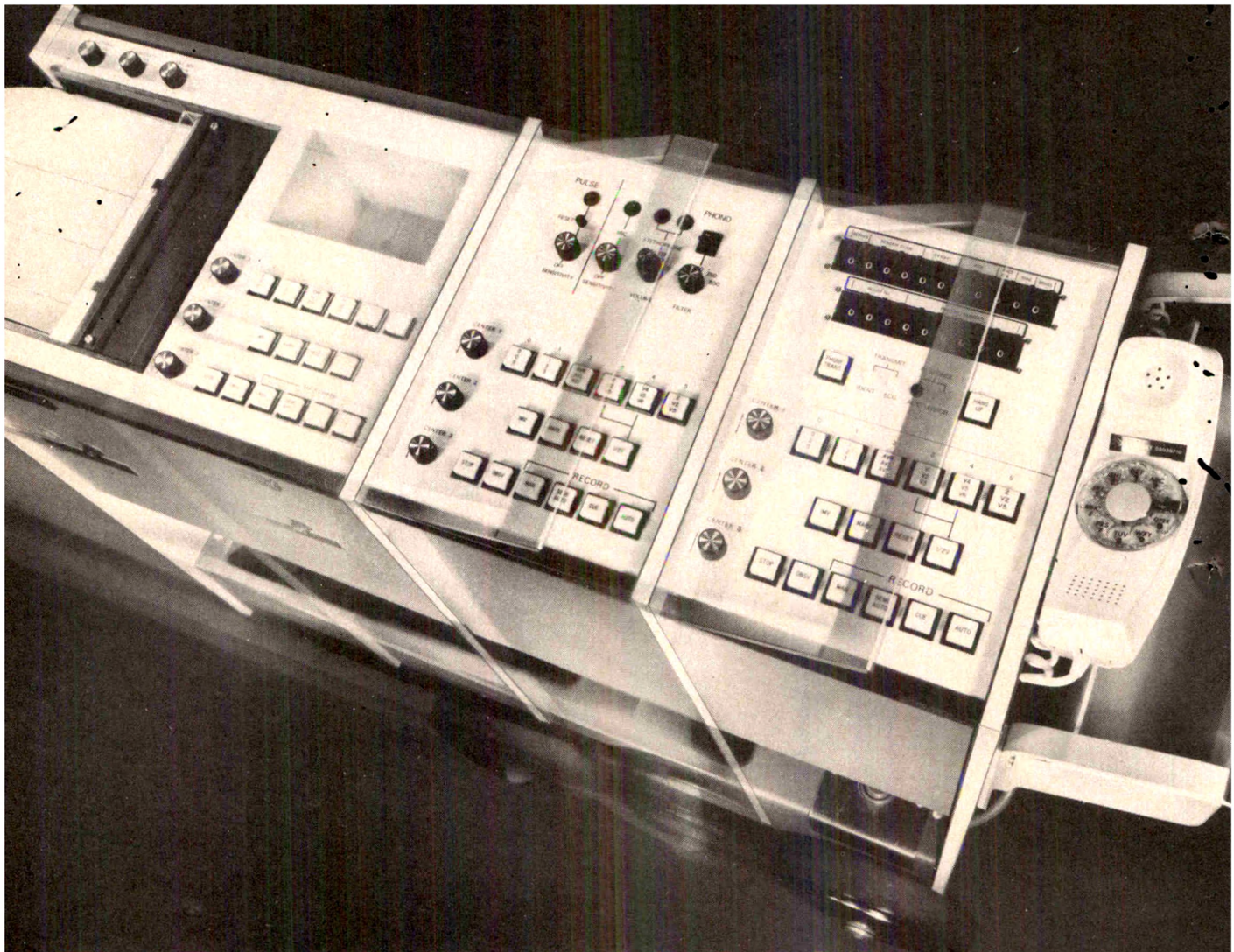

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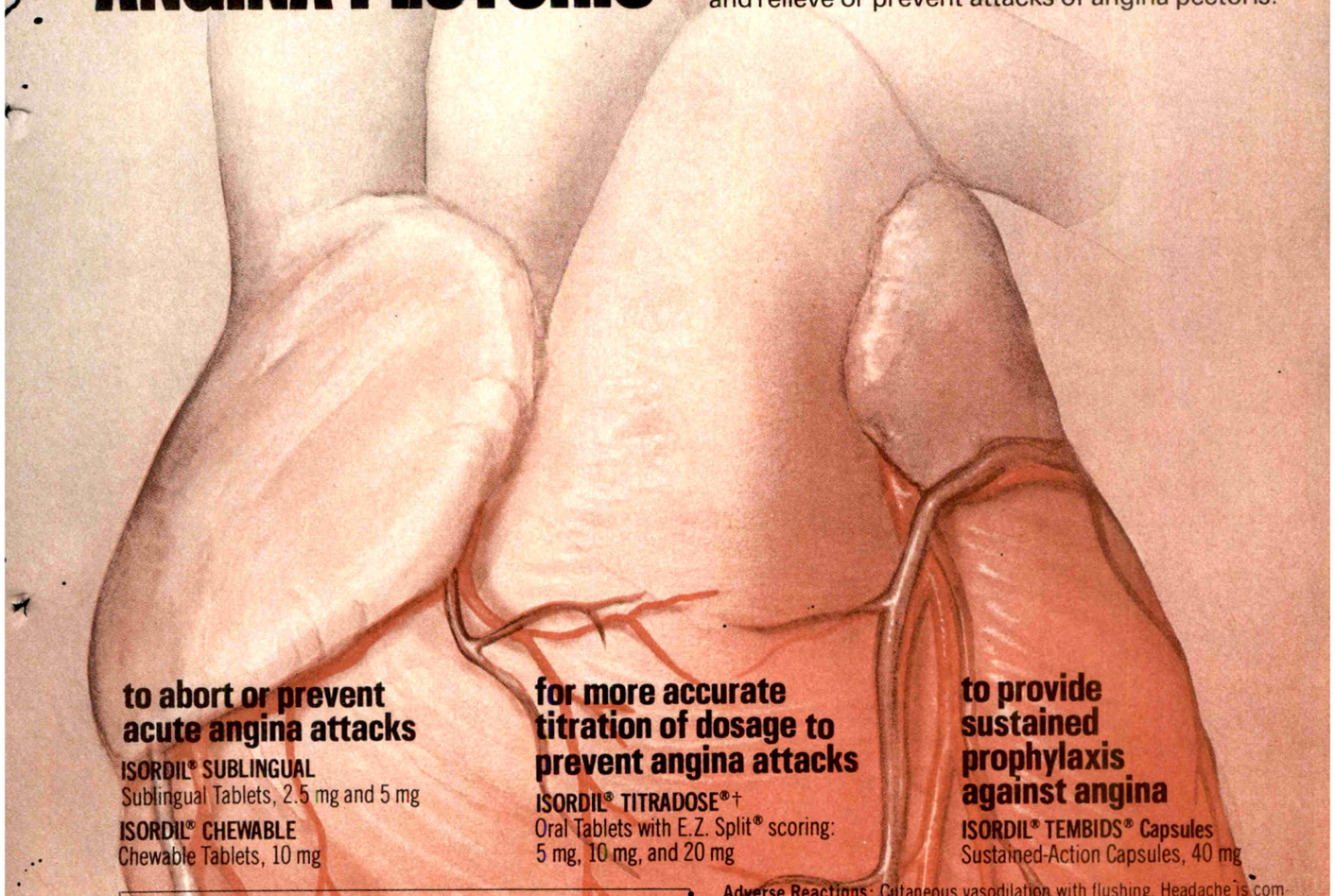

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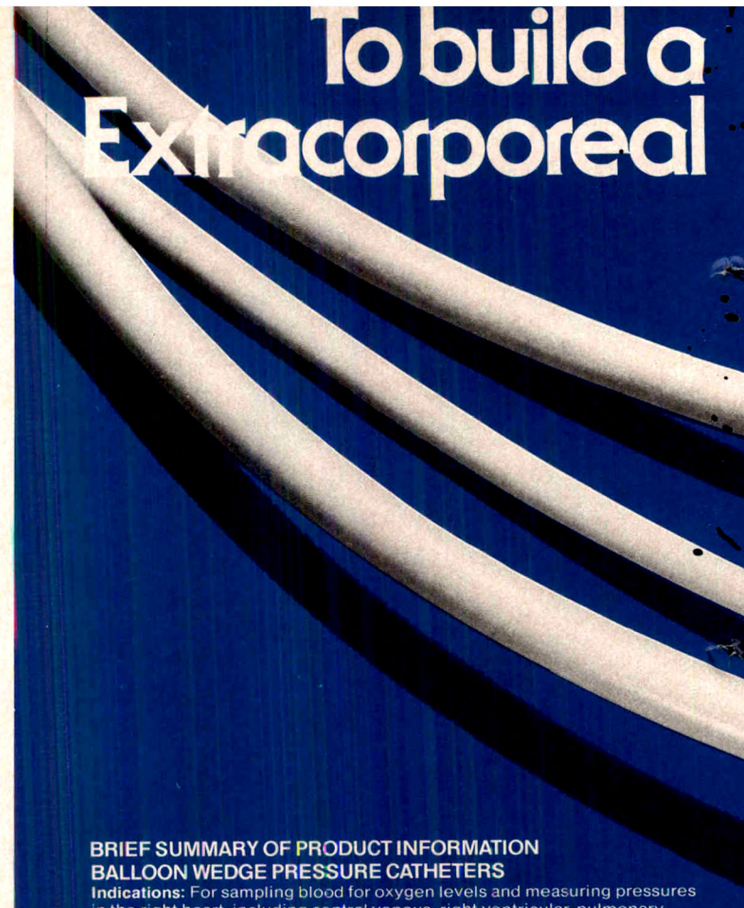

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Indications: For sampling blood for oxygen levels and measuring pressures in the right heart, including central venous, right ventricular, pulmonary artery, and pulmonary artery wedge pressure. Also indicated in anatomical cardiac defect cases to sample blood and measure pressures in any chambers that can be entered from the right heart. **Warning:** Pulmonary artery perforation, thrombosis, segmental pulmonary infarction, transient obstruction of the pulmonary outflow by the inflated balloon, balloon rupture without serious sequelae, premature ventricular contractions, and knotting of the catheter have been reported as complications of the use of balloon catheters. Balloon rupture with possible latex embolus is a potential complication in the use of balloon catheters. **Precaution:** In pressure monitoring at bedside when catheter has been introduced in an antecubital vein, patient's arm should be immobilized to reduce the possibility of catheter advancement due to arm motion.

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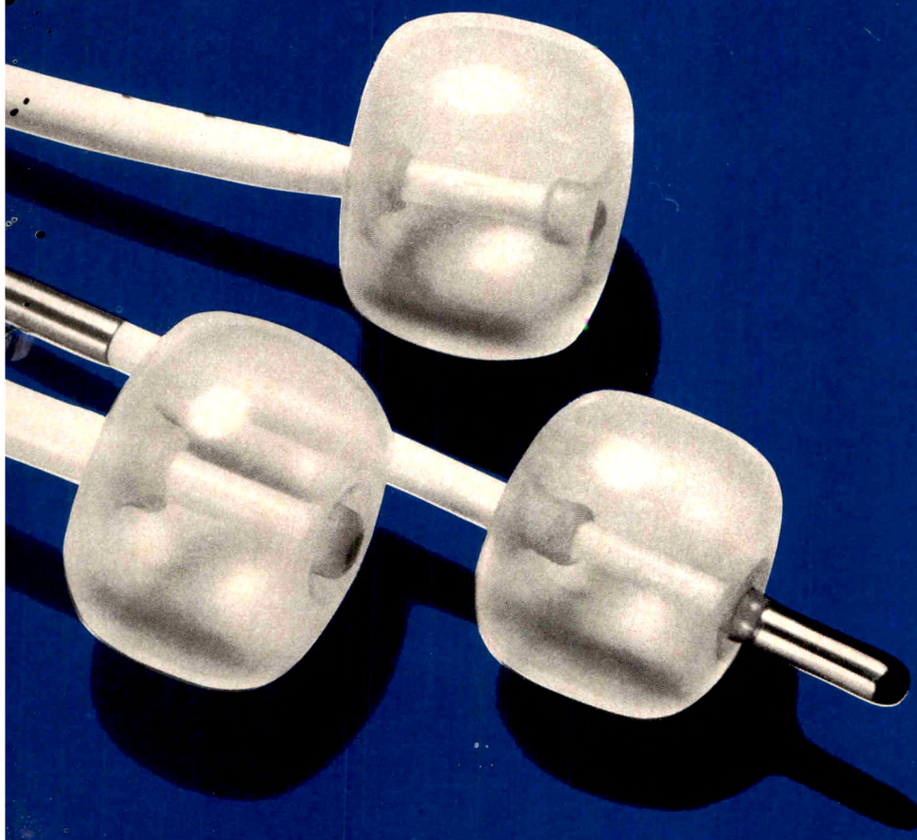
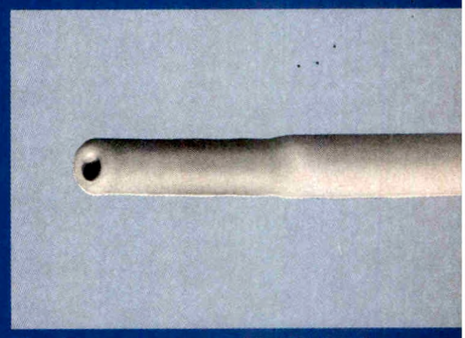
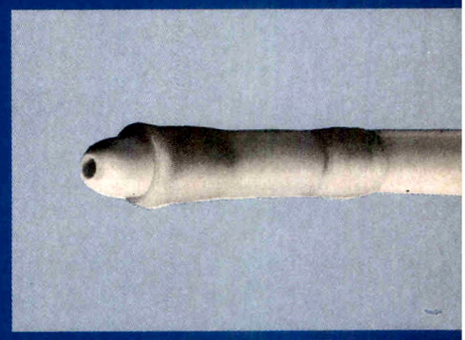




The Extracorporeal built-in tip, balloon deflated.



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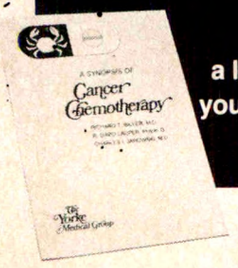
How to Keep Up with Drug Interaction in Cancer Chemotherapy



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A SYNOPSIS OF Cancer Chemotherapy

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- Structure
- Mechanism of Action
- Pharmacokinetics
- Toxicity
- Therapy
- Availability

The chemotherapeutic agents in the main listing section cover these categories:

- Alkylating Agents
- Antimetabolites
- Mitotic Inhibitors
- Antibiotics
- Miscellaneous (includes such drugs as Mithramycin, Mitotane, etc.)

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Description: Each tablet of Peritrate SA Sustained Action contains: pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Each tablet of Peritrate 40 mg contains pentaerythritol tetranitrate 40 mg. Each tablet of Peritrate 20 mg contains pentaerythritol tetranitrate 20 mg. Each tablet of Peritrate 10 mg contains pentaerythritol tetranitrate 10 mg. Peritrate (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

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Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.
Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.
Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe, persistent headaches may occur.

In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:

(a) Cutaneous vasodilatation with flushing.
(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.
(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

Dosage: Peritrate (pentaerythritol tetranitrate) may be administered in individualized doses up to 160 mg a day. Dosage can be initiated at one 10 mg or 20 mg tablet q.i.d. and titrated upward to 40 mg (two 20 mg tablets or one 40 mg tablet) q.i.d. one-half hour before or one hour after meals and at bedtime. Alternatively, Peritrate Sustained Action 80 mg can be administered on a convenient b.i.d. dosage schedule.
Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg—double-layer, biconvex, dark green/light green tablets in bottles of 100 (N 0047-0004-51) and 1000 (N 0047-0004-60). Also unit dose, package of 10 x 10 strips (N 0047-0004-11).

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STORE BETWEEN 59° and 86° F (15° and 30° C).
Animal Pharmacology: In a series of carefully designed studies in pigs, Peritrate (pentaerythritol tetranitrate) was administered for 48 hours before an artifically induced occlusion of a major coronary artery and for seven days thereafter. The pigs were sacrificed at various intervals for periods up to six weeks. The result showed a significantly larger number of survivors in the drug-treated group. Damage to myocardial tissue in the drug-treated survivors was less extensive than in the untreated group. Studies in dogs subjected to oligemic shock through progressive bleeding have demonstrated that Peritrate (pentaerythritol tetranitrate) is vasoactive at the postarteriolar level, producing increased blood flow and better tissue perfusion. These animal experiments cannot be translated to the drug's actions in humans.
Full information is available on request.

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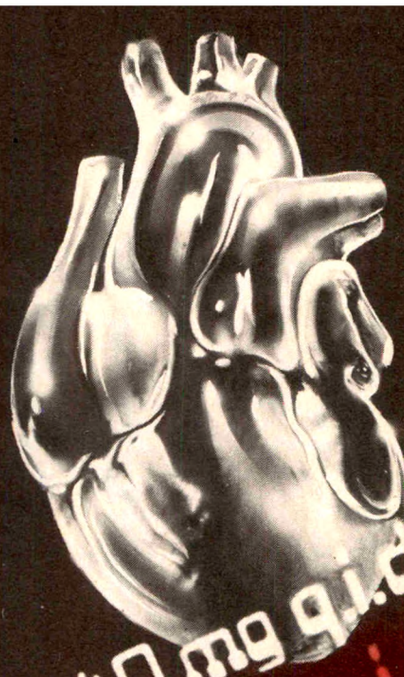

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In many angina* patients, response to Peritrate is optimum when dosage is titrated to its maximum

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*This drug has been evaluated as possibly effective for this indication.
See brief summary.

PE GP-74

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Aldactazide®

(spironolactone 25 mg./ hydrochlorothiazide 25 mg.)

WARNING

Spironolactone, an ingredient of Aldactazide, has been shown to be a tumorigen in chronic toxicity studies in rats (see *Warnings*). Aldactazide should be used only in those conditions described under *Indications*. Unnecessary use of this drug should be avoided.

Fixed-dose combination drugs are not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Indications: Cirrhosis of the liver accompanied by edema and/or ascites. Essential hypertension, edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate.

Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, hyperkalemia or acute or severe hepatic failure. Allergy to thiazide diuretics or to other sulfonamide-derived drugs.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactazide. Do not administer concurrently with other potassium-sparing diuretics. Sulfonamide derivatives including thiazides have been reported to exacerbate or activate systemic lupus erythematosus.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75 and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hypokalemia may develop as a result of profound diuresis, particularly when Aldactazide is used concomitantly with loop diuretics, glucocorticoids or ACTH. Transient elevation of BUN may occur. Dilutional hyponatremia or rarely low-salt syndrome may develop. Gynecomastia may develop and in rare instances some breast enlargement may persist.

Thiazides may alter the metabolism of uric acid and carbohydrates with possible hyperuricemia, gout and decreased glucose tolerance. Vascular responsiveness to norepinephrine is reduced. Thiazides may also increase the responsiveness to tubocurarine. Thiazides may decrease serum PBI levels and prolonged therapy may induce hypercalcemia and hypophosphatemia.

Spironolactone may and hydrochlorothiazide does cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. Breast feeding should be discontinued when Aldactazide is being used.

Adverse Reactions:

Associated with spironolactone: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established.

Associated with thiazides: Gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhea, abdominal cramps), purpura, thrombocytopenia, leukopenia, agranulocytosis, dermatologic symptoms (cutaneous eruptions, pruritus, erythema multiforme), paresthesia, acute pancreatitis, jaundice, dizziness, vertigo, headache, xanthopsia, photosensitivity, necrotizing angiitis, aplastic anemia, orthostatic hypotension, muscle spasm, weakness and restlessness.

Adverse reactions are usually reversible upon discontinuation of Aldactazide.

Dosage and Administration

Edema in adults: The usual maintenance dose is one tablet four times daily but may range from one to eight tablets daily depending on the response to the initial titration.

Edema in children: The usual daily maintenance dose should be that which provides 0.75 to 1.5 mg. of spironolactone per pound of body weight (1.65 to 3.3 mg./kg.).

Essential hypertension: Usually two to four tablets daily depending on results of the titration of the individual ingredients.

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Fixed-dose combination drugs are not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management.

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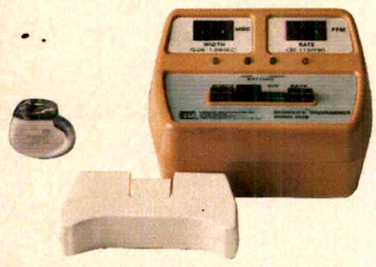

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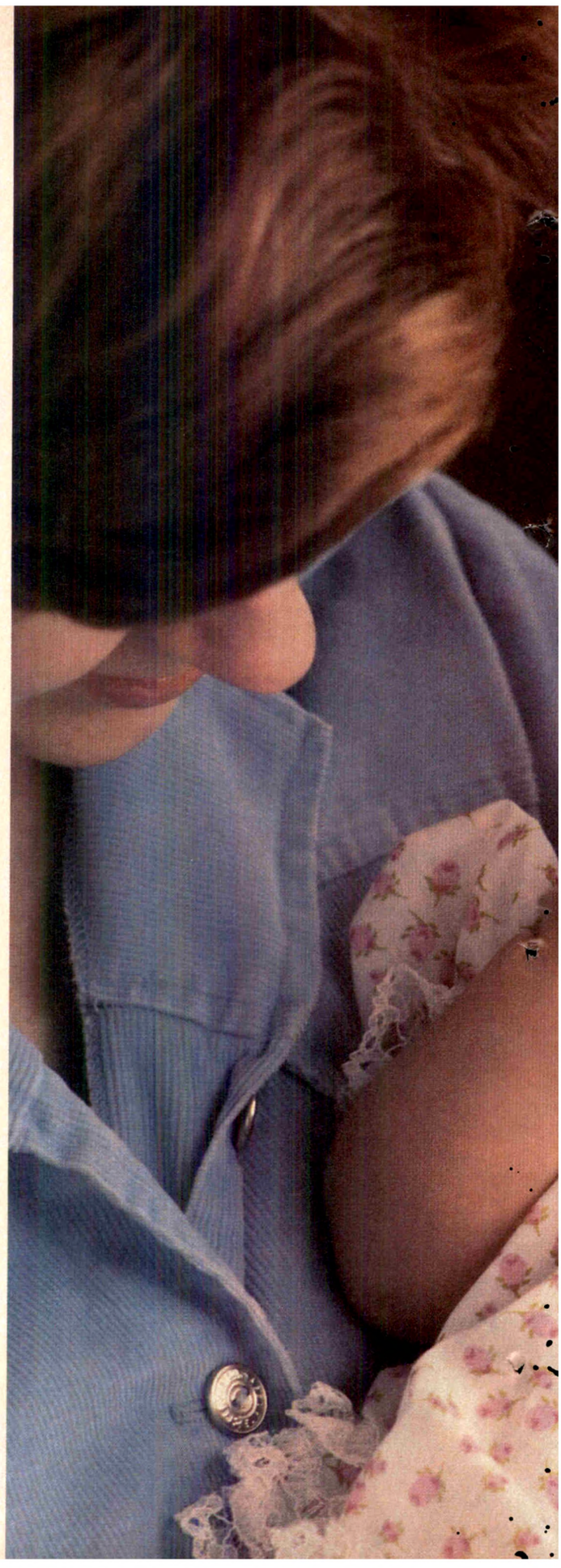

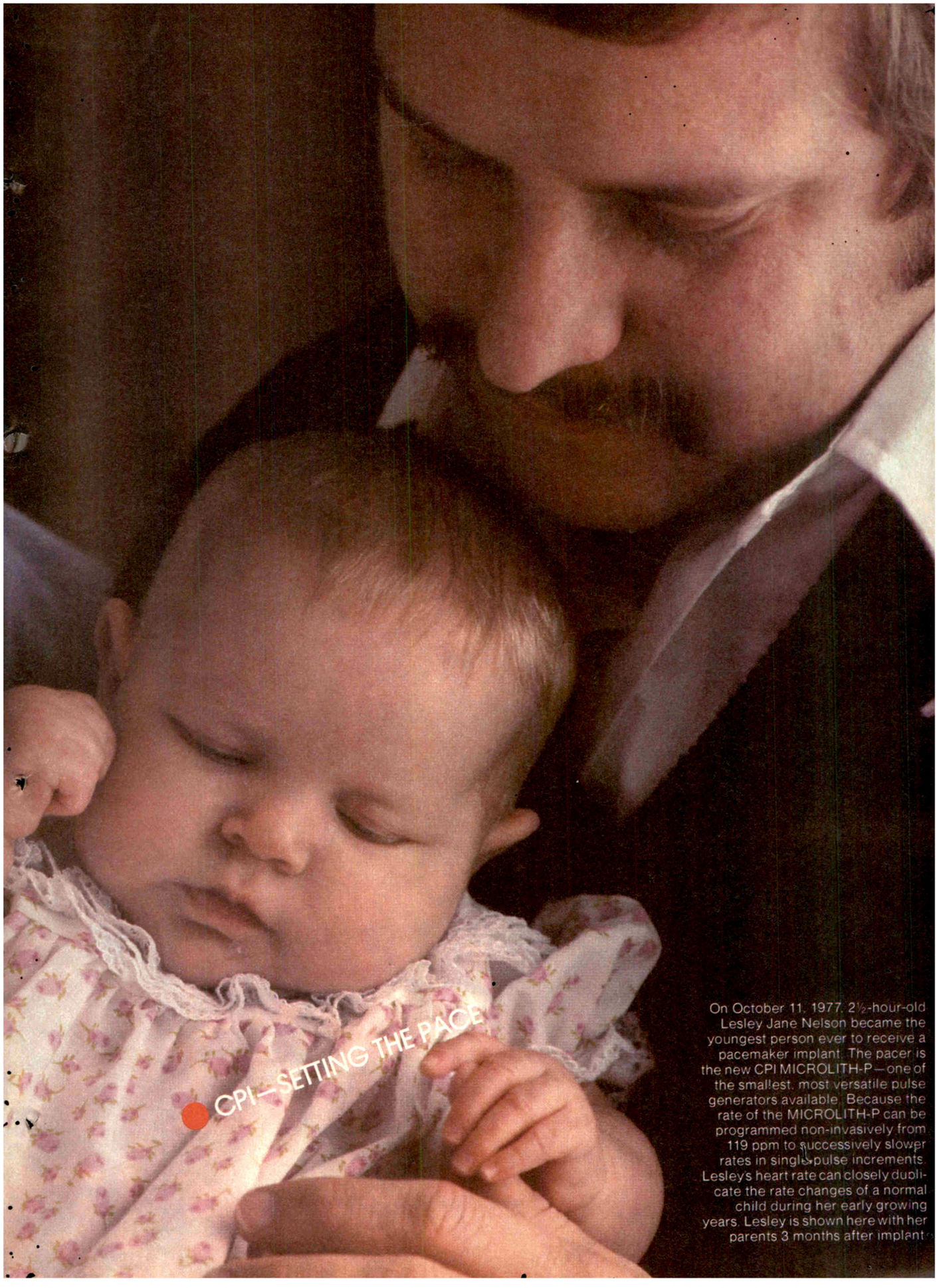

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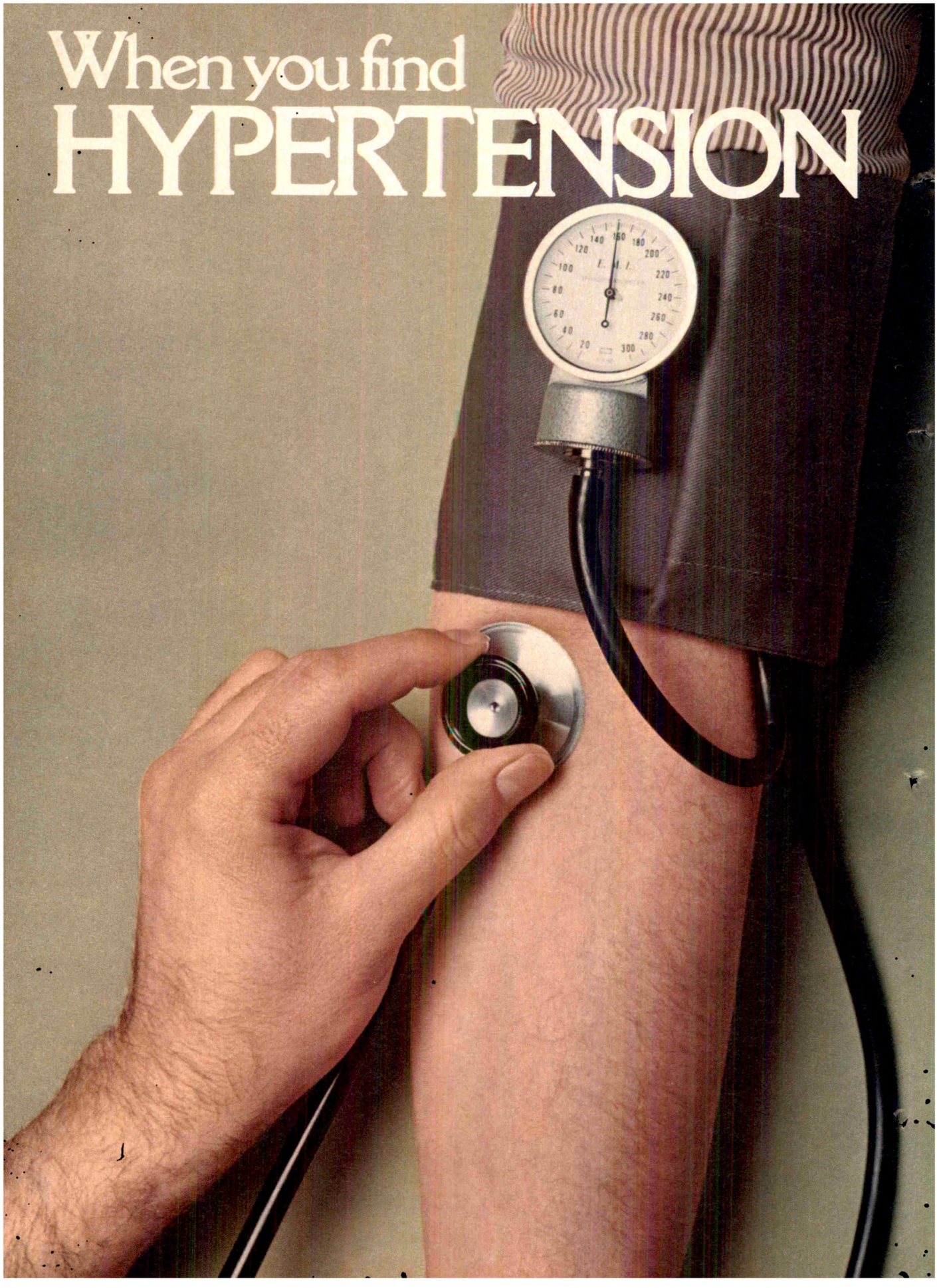
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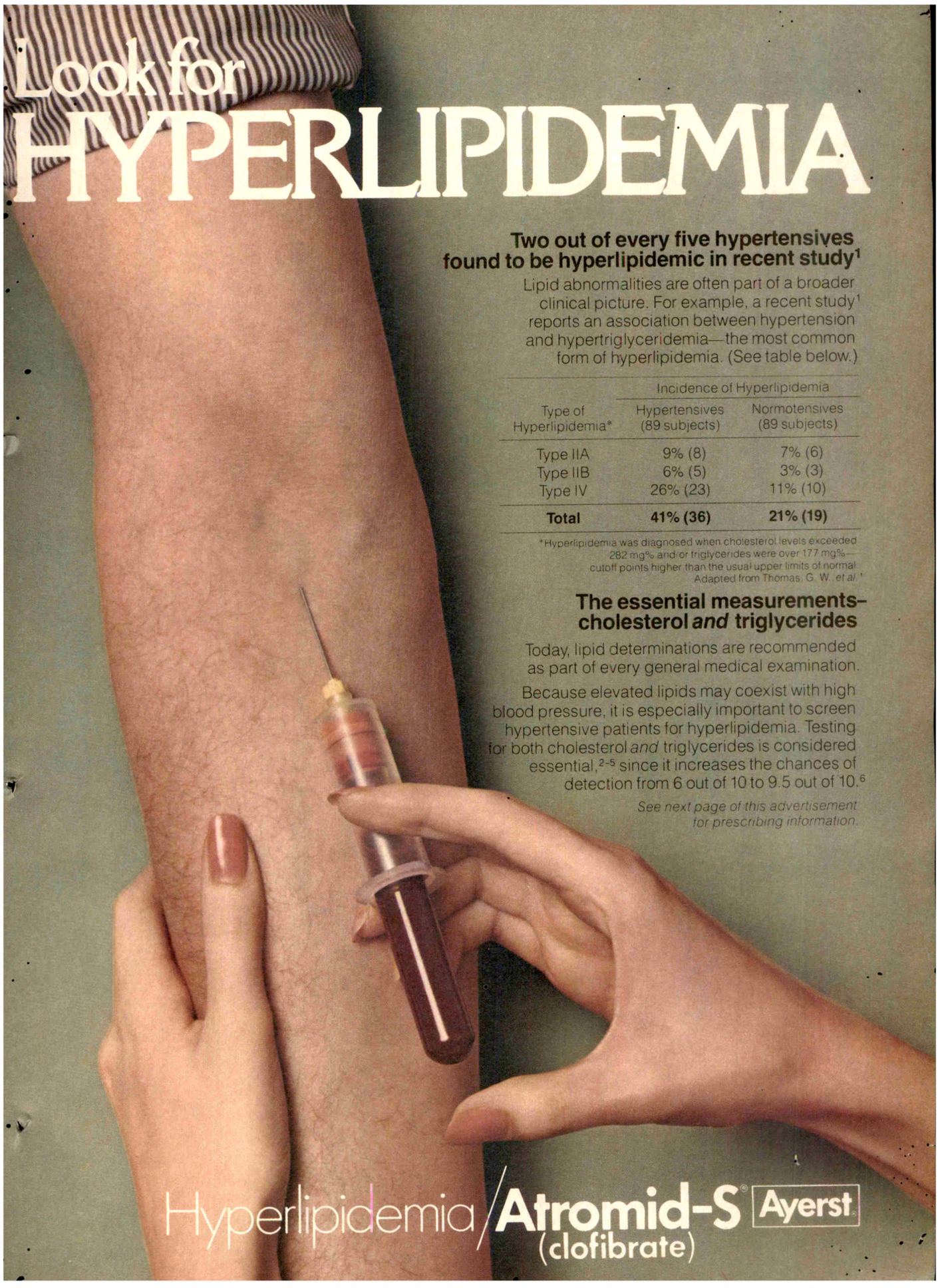


Look for HYPERLIPIDEMIA

Two out of every five hypertensives found to be hyperlipidemic in recent study[1]

Lipid abnormalities are often part of a broader clinical picture. For example, a recent study[1] reports an association between hypertension and hypertriglyceridemia—the most common form of hyperlipidemia. (See table below.)

Type of Hyperlipidemia*	Incidence of Hyperlipidemia	
	Hypertensives (89 subjects)	Normotensives (89 subjects)
Type IIA	9% (8)	7% (6)
Type IIB	6% (5)	3% (3)
Type IV	26% (23)	11% (10)
Total	**41% (36)**	**21% (19)**

*Hyperlipidemia was diagnosed when cholesterol levels exceeded 282 mg% and/or triglycerides were over 177 mg%—cutoff points higher than the usual upper limits of normal. Adapted from Thomas, G. W., *et al.*[1]

The essential measurements–cholesterol *and* triglycerides

Today, lipid determinations are recommended as part of every general medical examination.

Because elevated lipids may coexist with high blood pressure, it is especially important to screen hypertensive patients for hyperlipidemia. Testing for both cholesterol *and* triglycerides is considered essential,[2-5] since it increases the chances of detection from 6 out of 10 to 9.5 out of 10.[6]

See next page of this advertisement for prescribing information.

Hyperlipidemia/**Atromid-S**® (clofibrate) Ayerst

When you find HYPERTENSION Look for HYPERLIPIDEMIA

Atromid-S® (clofibrate)

(For full prescribing information, see package circular.)

ATROMID-S® Brand of clofibrate

Antilipidemic agent for reduction of elevated serum lipids

INDICATIONS: ATROMID-S is indicated as adjunctive therapy in patients who do not respond adequately to diet and other measures for the reduction of elevated serum cholesterol (especially the beta lipoprotein fraction) and/or triglycerides. Clofibrate appears to have a greater depressant effect on the very low density lipoproteins (S_f 20-400) rich in triglycerides than the low density lipoproteins (S_f 0-20) rich in cholesterol.

ATROMID-S is also indicated for treatment of patients with xanthoma tuberosum associated with hyperlipidemia. The skin lesions frequently regress with clofibrate.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CONTRAINDICATIONS: Clofibrate is contraindicated in pregnant women. While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than that found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

It is contraindicated in lactating women since it is not known if clofibrate is secreted in the milk.

It is contraindicated in patients with clinically significant hepatic or renal dysfunction.

It is contraindicated in patients with primary biliary cirrhosis since it may raise the already elevated cholesterol in these cases.

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Strict birth control procedures must be exercised by women of childbearing potential. In patients who plan to become pregnant, clofibrate should be withdrawn several months before conception. Because of the possibility of pregnancy occurring despite birth control precautions in patients taking clofibrate, the possible benefits of the drug to the patient must be weighed against possible hazards to the fetus.

Administration of clofibrate to mice and rats in long-term studies at eight times the human dose resulted in a higher incidence of liver tumors than in controls. Lower doses were not studied. Although the relevance of this finding to humans is not known at this time, it cannot be dismissed especially since this drug is intended for long-term administration. ATROMID-S should be used only in patients with hyperlipidemia who do not respond adequately to dietary intervention.

PRECAUTIONS: Before instituting therapy with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.

Because of the long-term administration of a drug of this nature, adequate baseline studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be obtained during the first few months of ATROMID-S administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, the drug should be employed for longer periods (even up to one year) provided that there is a reduction in the size and/or number of the xanthomata.

Subsequent serum lipid determinations should be done to detect a paradoxical rise in serum cholesterol or triglyceride levels. Clofibrate will not alter the seasonal variations of serum cholesterol peak elevations in midwinter and late summer and decreases in fall and spring. If the drug is discontinued, the patient should be placed on an appropriate hypolipidemic diet, and his serum lipids should be monitored until stabilized, as a rise in these values to or above the original baseline may occur.

During clofibrate therapy, frequent serum transaminase determinations and other liver function tests should be performed since the drug may produce abnormalities in these parameters. These effects are usually reversible when the drug is discontinued. Hepatic biopsies are usually within normal limits. If the hepatic function tests steadily rise or show excessive abnormalities, the drug should be withdrawn. Therefore use with caution in those patients with a past history of jaundice or hepatic disease.

Clofibrate may produce "flu like" symptoms (muscular aching, soreness, cramping). The physician should differentiate this from actual viral and/or bacterial disease.

Use with caution in patients with peptic ulcer since reactivation has been reported. Whether this is drug-related is unknown.

Complete blood counts should be done periodically since anemia, and more frequently, leukopenia have been reported in patients who have been taking clofibrate.

Various cardiac arrhythmias have been reported with the use of clofibrate.

Several investigators have observed in their studies that clofibrate may produce a decrease in cholesterol linoleate but an increase in palmitoleate and oleate, the latter being considered atherogenic in experimental animals. The significance of this finding is unknown at this time.

ADVERSE REACTIONS: Of the pertinent reactions, the most common is nausea. Less frequently encountered gastrointestinal reactions are vomiting, loose stools, dyspepsia, flatulence, and abdominal distress. Reactions reported less often than gastrointestinal ones are headache, dizziness, and fatigue; muscle cramping, aching, and weakness; skin rash, urticaria, and pruritus; dry brittle hair, and alopecia.

The following reported adverse reactions are listed alphabetically by systems:

Cardiovascular
- Increased or decreased angina
- Cardiac arrhythmias
- Both swelling and phlebitis at site of xanthomas

Dermatologic
- Skin rash
- Alopecia
- Allergic reaction including urticaria
- Dry skin and dry brittle hair
- Pruritus

Gastrointestinal
- Nausea
- Diarrhea
- Gastrointestinal upset (bloating, flatulence, abdominal distress)
- Hepatomegaly (not associated with hepatotoxicity)
- Gallstones
- Vomiting
- Stomatitis and gastritis

Genitourinary
- Impotence and decreased libido
- Findings consistent with renal dysfunction as evidenced by dysuria, hematuria, proteinuria, decreased urine output. One patient's renal biopsy suggested "allergic reaction."

Hematologic
- Leukopenia
- Potentiation of anticoagulant effect
- Anemia
- Eosinophilia

Musculoskeletal
- Myalgia (muscle cramping, aching, weakness)
- "Flu like" symptoms
- Arthralgia

Neurologic
- Fatigue, weakness, drowsiness
- Dizziness
- Headache

Miscellaneous
- Weight gain
- Polyphagia

Laboratory Findings
- Abnormal liver function tests as evidenced by increased transaminase (SGOT and SGPT), BSP retention, and increased thymol turbidity
- Proteinuria
- Increased creatine phosphokinase

Reported adverse reactions whose direct relationship with the drug has not been established: peptic ulcer, gastrointestinal hemorrhage, rheumatoid arthritis, tremors, increased perspiration, systemic lupus erythematosus, blurred vision, gynecomastia, thrombocytopenic purpura.

DOSAGE AND ADMINISTRATION: *Initial:* The recommended dosage for adults is 2 g daily, in divided doses. Some patients may respond to a lower dosage.

Maintenance: Same as for initial dosage.

Note: In children, insufficient studies have been done to show safety and efficacy.

DRUG INTERACTIONS: Caution should be exercised when anticoagulants are given in conjunction with ATROMID-S. The dosage of the anticoagulant should be reduced usually by one-half (depending on the individual case) to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has been stabilized.

MANAGEMENT OF OVERDOSAGE: While there has been no reported case of overdosage, should it occur, symptomatic supportive measures should be taken.

HOW SUPPLIED: ATROMID-S—No. 243—Each capsule contains 500 mg clofibrate, in bottles of 100.

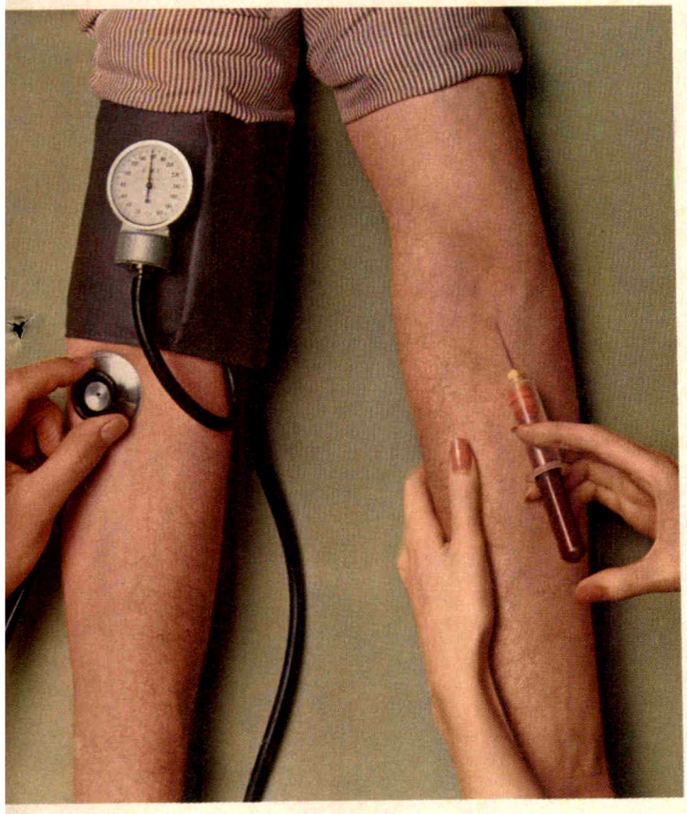
References: 1. Thomas, G. W., *et al.*: Br. Med. J. *2*:805 (Sept. 24) 1977. **2.** Ahrens, E. H., Jr.: Ann. Intern. Med. *85*:87 (July) 1976. **3.** Council on Foods and Nutrition: J.A.M.A. *222*:1647 (Dec. 25) 1972. **4.** Scheig, R.: Conn. Med. *39*:71 (Feb.) 1975. **5.** Letters to the Editor: Current Prescribing (July) 1977, p. 15. **6.** Fredrickson, D. S., *et al.*, in Holmes, W. L., Carlson, L. A., and Paoletti, R.: Drugs Affecting Lipid Metabolism, Vol. 4, New York, Plenum Press, 1969, p. 314. **7.** Brown, H. B., Lewis, L. A., and Page, I. H.: Clin. Pharmacol. Ther. *17*:171 (Feb.) 1975. **8.** Gelfand, M. L., and Garbor, M.: Exhibit, American College of Cardiology Meeting, New Orleans, La., Feb. 21-Mar. 1, 1970. **9.** Zelis, R., *et al.*: J. Clin. Invest. *49*:1007 (May) 1970. **10.** Levy, R. I., *et al.*: Ann. Intern. Med. *77*:267 (Aug.) 1972. **11.** Berkowitz, D.: J.A.M.A. *218*:1002 (Nov. 15) 1971. **12.** Lorenzo, E. M., *et al.*: Curr. Ther. Res. *22*:147 (July, Sect. 2) 1977.

Ayerst®
Ayerst Laboratories
New York, N.Y. 10017

In hyperlipidemia
When diet alone is not enough

Atromid-S®
(clofibrate) Capsules 500 mg

The most widely prescribed antilipemic agent–significantly lowers serum levels of cholesterol and/or triglycerides



Proved effective in study after study

In clinical studies involving patients with drug-responsive hyperlipoproteinemia, diet plus ATROMID-S (clofibrate) lowered serum cholesterol levels from 22% to as much as 52% and reduced triglyceride values over a range of 19% to 80%.[7-12]

Patient acceptance is generally good

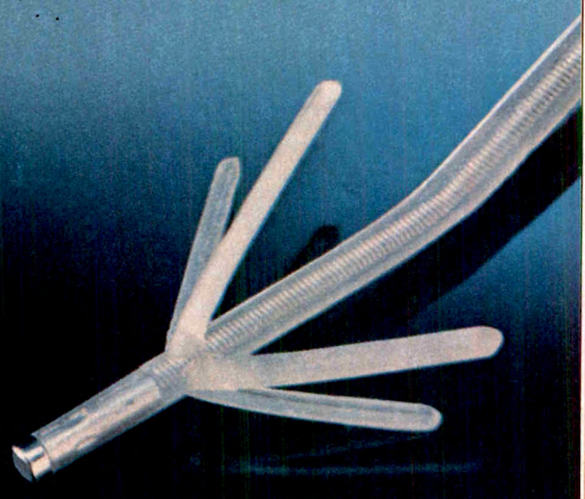
In more than a decade of use, clofibrate has been generally well tolerated. Major adverse effects are primarily gastrointestinal, with nausea being predominant. Other G.I. reactions include loose stools, flatulence, abdominal distress, and, infrequently, gallstones. Less common reactions include muscle cramping, myalgia, and alopecia. Please see "Important Note" below and Warning on concomitant anticoagulant usage in prescribing information on adjacent page.

AN IMPORTANT NOTE: It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

See adjacent page of this advertisement for prescribing information.

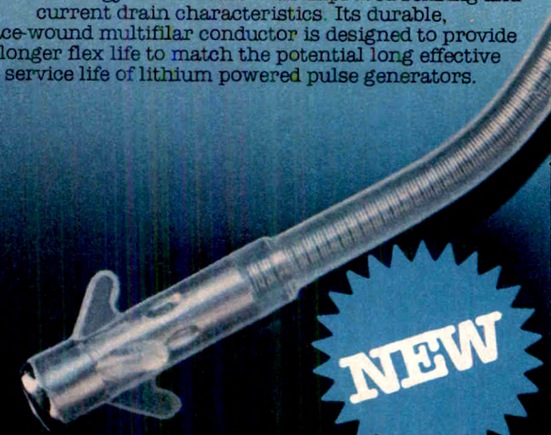
An Endocardial Tined Ventricular Lead.

The Medtronic® 6950 and 6951 unipolar and bipolar tined leads feature four integral silicone rubber tines that protrude from the lead body just proximal to the tip electrode. These tines were designed to provide better acute lead stability and reduce chronic lead dislodgement by latching onto the papillary musculature or the trabeculae of the right ventricle. The large surface area provided by the tines should also enhance the stability afforded by fibrosis.



A Small, Durable Endocardial Tined Lead.

The newest members of the Tenax™ family of self-anchoring leads – the 6961 and 6962 unipolar and bipolar leads – feature shorter, smaller tines and small tip diameter (8 French; approximately 10 French with tines folded) enabling the physician to use the more common cephalic approach. Though small, the soft, pliable tines are still long enough to become securely anchored in one or more of the interstitial spaces formed by the trabeculae of the right ventricular chamber. The lead's ring-tipped electrode provides optimum energy to the heart with improved sensing and current drain characteristics. Its durable, space-wound multifilar conductor is designed to provide a longer flex life to match the potential long effective service life of lithium powered pulse generators.



NEW

TOUGH & TENACIOUS

The TENAX™ Family of Self-Anchoring Leads from Medtronic.

Our entire family of Medtronic Tenax™ leads has one common trait:
Tenacious, positive-anchoring lead tips.
Tips designed to minimize dislodgement problems associated with standard endocardial pacing leads.
Tips that stay where you put them.

MEDTRONIC IMPLANTABLE PACING LEADS

Intended Use

Medtronic implantable pacing leads are designed to be used with Medtronic pulse generators as part of a cardiac pacing system (see product labeling for specific directions regarding applications).

Contraindications

Endocardial pacing leads are contraindicated in the presence of tricuspid valvular disease.

Myocardial leads are contraindicated for a patient whose myocardium is thin-walled, suffused with fat, or infarcted in the area of electrode placement.

Myocardial leads may be contraindicated in the older high risk patients with a low tolerance to general anesthesia.

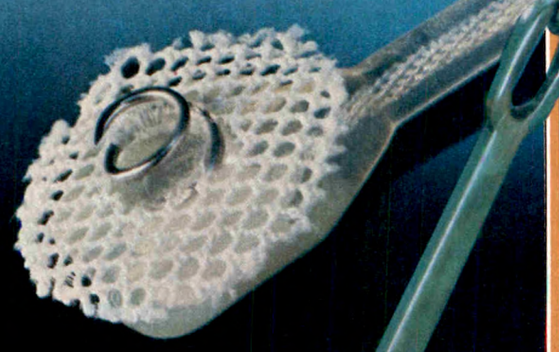
Atrial J-leads are contraindicated in the absence of a right atrial appendage.

Warnings

An implanted lead constitutes a direct, low resistance current path to the myocardium.

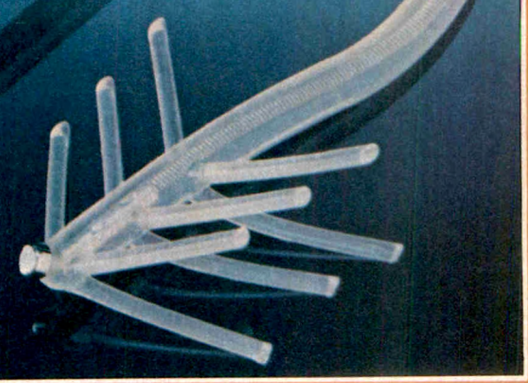
A Unique Sutureless Myocardial Lead.

Our Model 6917 sutureless lead is the largest selling pacing lead worldwide. Its unique screw-in electrode, introduced in 1973, eliminates the necessity of making a stab wound and suturing to the myocardium. The electrode tip is secured by simply rotating it into the myocardium. The 6917A has been successfully installed on either the right or left ventricle using a variety of surgical approaches such as limited thoracotomy, subxiphoid, transxiphoid, and transmediastinal, in some cases using only local anesthesia.



A Tined Endocardial Atrial J-Shaped Lead.

The Medtronic 6991 unipolar and 6990 bipolar leads are molded into a J configuration to facilitate placement and lodging into the right atrial appendage. During insertion, the J tip is straightened by means of lead stylets. The distal end of the J contains a series of nine silicone rubber tines; the electrode tip is canted inward so the force exerted by the tines will enable the electrode to contact the endocardial surface of the atrium. After the lead tip has been advanced into the desired position, the stylets are partially withdrawn to allow the lead to assume its natural J shape. The tines are fixed into the atrial appendage by becoming anchored in one or more of the interstitial spaces formed by trabeculae.



For further information on the Medtronic Tenax™ lead family, contact your Medtronic, Inc. representative or write for a complete technical brochure.

Medtronic, Inc.
3055 Old Highway Eight, P.O. Box 1453
Minneapolis, Minnesota 55440

Medtronic

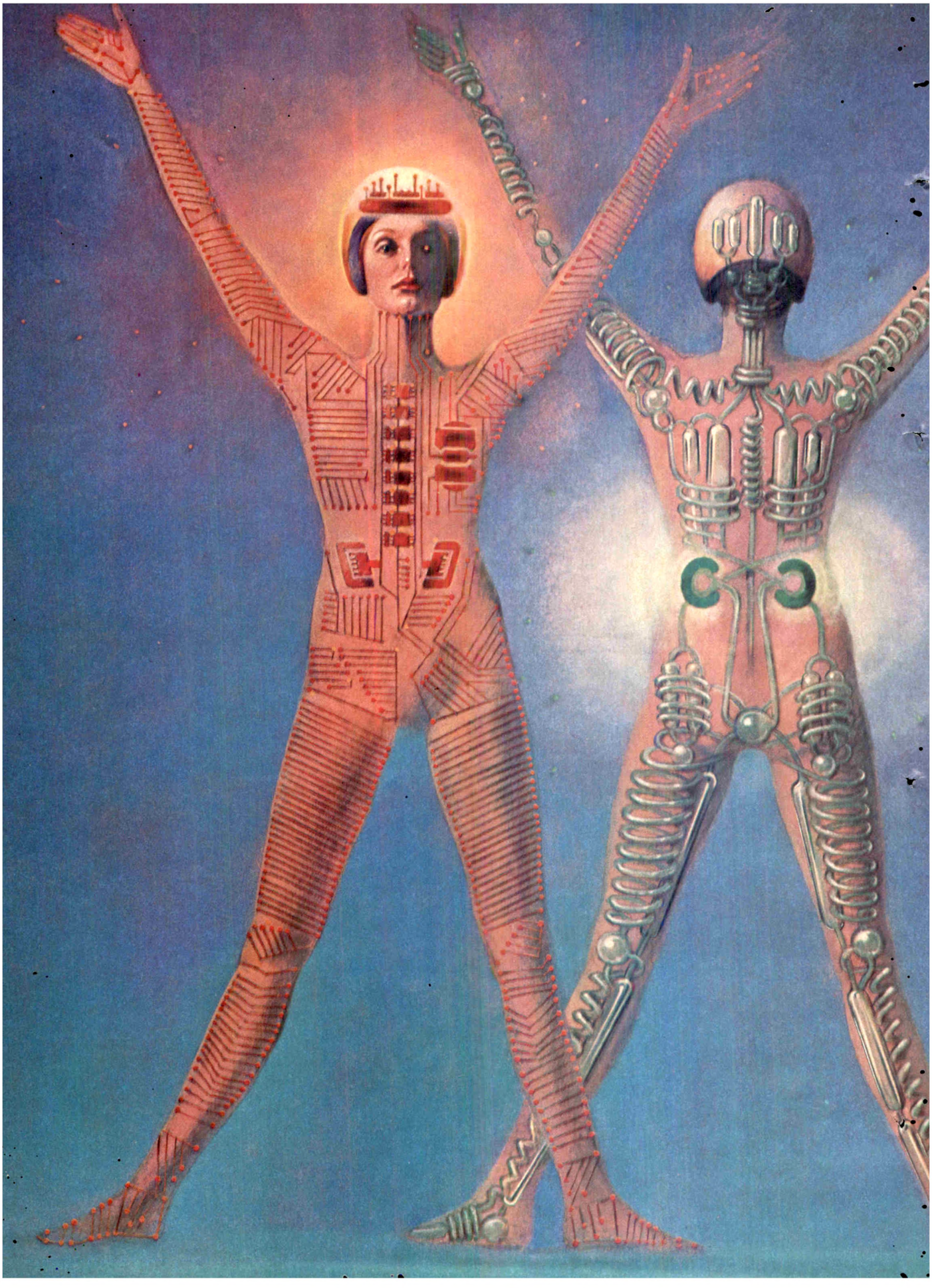
Helping You Help
The Pacemaker Patient

During the connection and testing procedures, only battery-powered pulse generators should be used with the lead system to protect against ventricular fibrillation induced by alternating current leakage. Extreme caution must be taken to properly ground all line-powered equipment used in the vicinity of the patient.

Precautions
The pacing system may cease to function due to lead-related problems such as displacement, fracture, fibrotic tissue formation and elevated thresholds.

Side Effects
Body rejection phenomena, infection, erosion or migration through body tissue, transvenous lead-related thrombosis, embolism.

How Supplied
Medtronic permanent implantable leads are supplied sterilized and individually wrapped. Medtronic pacing leads are designed to be used with Medtronic pulse generators.



Help your patient into the future
Combipres in hypertension
Combipres works efficiently, smoothly.
Brings blood pressure down...keeps it down over the long-term*.
Life therapy...not life sentence
91% of patients tolerated it well in clinical trials.[1]
Low incidence of impotence, depression, orthostatic hypotension.
Its most common side effects are dry mouth, drowsiness, and sedation. They tend to diminish with continued use, and may be alleviated by giving the larger portion of the divided dose at bedtime.
Combipres® .1 and .2
Each tablet contains:
Catapres® (clonidine hydrochloride)
0.1 or 0.2 mg. and chlorthalidone, 15 mg
There's a future in it.
Please see brief summary of the prescribing information on last page of this ad for warnings, precautions, and adverse reactions.
As with other antihypertensives containing diuretic agents, hypokalemia, hyperuricemia, and hyperglycemia may occur.
*Combipres is not indicated for initial therapy of hypertension. See box warning on next page.

Combipres® .1 and .2

Each tablet contains:
Catapres® (clonidine hydrochloride) 0.1 or 0.2 mg, and chlorthalidone, 15 mg

in hypertension

...there's a future in it

Warning: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Indication: The drug is indicated in the treatment of hypertension (see box warning).

Contraindications: Patients with known hypersensitivity to chlorthalidone and patients with severe renal or hepatic diseases.

Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine.

Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

A decreased glucose tolerance evidenced by hyperglycemia and glycosuria may develop inconsistently. This condition, usually reversible on discontinuation of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed should be checked regularly.

As with other diuretic agents hypokalemia may occur (see Precautions). Hyperuricemia may be observed on occasion and acute attacks of gout have been precipitated. In cases where prolonged and significant elevation of blood uric acid concentration is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Idiosyncratic drug reactions such as aplastic anemia, thrombocytopenia, leukopenia, agranulocytosis, and necrotizing angiitis have occurred, but are rare.

The remote possibility of pancreatitis should be considered when epigastric pain or unexplained gastrointestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reported with this general class of compounds include: jaundice, xanthopsia, paresthesia and photosensitization.

Overdosage: *Catapres (clonidine hydrochloride):* Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

How Supplied: Combipres® 0.1 (Each tablet contains clonidine hydrochloride 0.1 mg + chlorthalidone,15 mg). It is available as pink, oval, single-scored compressed tablets in bottles of 100.

Combipres® 0.2 (Each tablet contains clonidine hydrochloride 0.2 mg + chlorthalidone,15 mg). It is available as blue, oval, single-scored compressed tablets in bottles of 100.

For complete details, please see full prescribing information.

1. Data on file at Boehringer Ingelheim Ltd.

Boehringer Ingelheim
Boehringer Ingelheim Ltd.
Ridgefield, CT 06877

4 critical criteria in choosing a Holter service

Before you select a Holter service, make sure it meets these 4 important standards. Telemed does!

1. Technician Specialization.

Scanning a long term ECG tape is a specialty requiring intense concentration.

Telemed makes sure this concentration is not disturbed. Holter monitoring is the only responsibility our Holter technicians have. This not only sharpens their focus, but also better enables them to spot meaningful events, morphologic changes, arrhythmias, even slight abnormalities.

2. Non-Fatiguing Technician Workload.

Volume is important to any Holter scanning service, but Telemed never puts quantity ahead of quality. Telemed's "Always Alert" Policy limits the number of tapes a Holter technician can scan per day. This minimizes fatigue, so technicians are more alert, ready to recognize changes no matter how slight.

3. Emergency Alert.

Telemed provides a double assurance that you are notified immediately if any life threatening abnormalities appear. Double assurance because both the Holter technician and a staff cardiologist review each scan for events which require your immediate attention. You are notified at once when such events are spotted.

4. Continuous Dual-Channel Equipment.

The Telemed Holter Scanning Service features state-of-the-art, continuous dual-channel monitoring equipment for greater reliability in arrhythmia detection and in the diagnosis of coronary artery disease.

Telemed's Holter Scanning Service includes tapes, patient diaries, mailers, service and maintenance. Plus Telemed trains your personnel at no extra charge. For full details on how Telemed Holter Scanning can help you help your patients, call or write Telemed today.

Telemed's Holter Scanning Service meets all four crucial standards.

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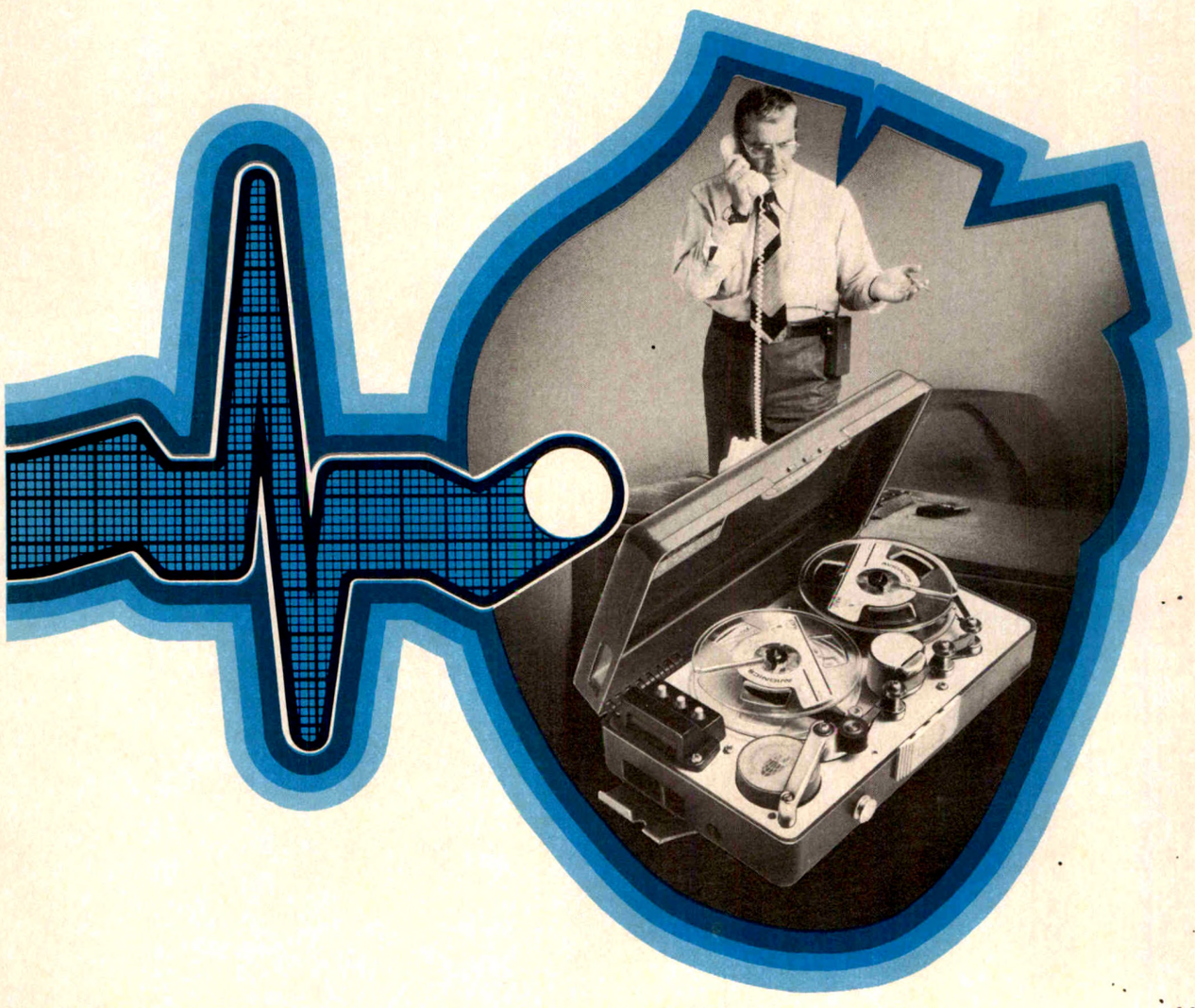


A45

For nine and a half years Quinaglute® (quinidine gluconate) has kept the pace for Mary L.*

*Based on actual case history (photos posed by professional model).

Time-proven Quinaglute® DURA-TABS® (quinidine gluconate) 324 mg keeps the pace for patients with cardiac arrhythmias

For Mary L. and hundreds of thousands of cardiac patients, QUINAGLUTE® Dura-Tabs® have helped maintain the pace of normal sinus rhythm over long-term therapy. In the 19 years since its introduction, QUINAGLUTE has amassed an impressive clinical record of therapeutic efficacy, safety and patient acceptance.

Classic antiarrhythmic therapy—
Time-proven for efficacy

- in the management of PAC, PVC and atrial fibrillation

Time-proven for reliability

- in maintaining quinidine plasma levels for 8 to 12 hours
- in providing sustained control without peaks and valleys in plasma levels

Time-proven for safety

- low incidence of G.I. irritation
- 19 years of patient and physician acceptance

Time-proven for patient compliance

- convenient dosage schedule that's easy to remember: 1 to 2 Dura-Tabs® every 8 or 12 hours
- h.s. dose helps avoid early morning reversion

Contraindications: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.

Partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. Renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects, ventricular premature beats, ventricular tachycardia or flutter while on the drug.

Marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis. Idiosyncrasy or hypersensitivity to quinidine.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate.

Precautions: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy.

Quinidine in large doses may reduce the contractile force of the heart, therefore, extreme caution should be exercised in using the drug in patients with severe heart disease, hypotension or digitalis intoxication.

It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

Adverse reactions: Cinchonism, tinnitus, decreased auditory acuity, vertigo, headache, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis, hypotension, respiratory distress, and gastrointestinal disturbances. 10-71

Cooper Laboratories, Inc.
Wayne, New Jersey 07470

For full information please refer to package insert.

Intermedics Inc.

Albert P. Beutel, II
President

July 1, 1978

To: The American Journal of Cardiology and its Editor,
Dr. Simon Dack

We wish to extend our heartiest congratulations upon this anniversary marking your twenty years of contribution in the area of medical publishing. The field of cardiology has indeed been fortunate to be represented by such a respected journal and distinguished editor over these past twenty years.

While those of us involved in the health care industry are well aware of your accomplishments, the deepest appreciation of your efforts will perhaps go unheralded by those who have benefited most, the patients. Through the critical review and dissemination of vital medical information, The American Journal of Cardiology has undoubtedly helped to save thousands of lives.

The continued growth of your journal, while maintaining the highest standards of quality, embodies the same kind of dedication and service to human health care that we strive to achieve at Intermedics. Dedication of this type and the ensuing progress it helps create will ensure continuing success for us all in the future.

With sincere congratulations,

Albert P Beutel

P.O. Box 617 Freeport, Texas 77541 • Phone (713) 233-8611 • Toll Free: 1: (800) 231-2330

The American Journal of CARDIOLOGY®

Simon Dack, MD, FACC

THE 20TH ANNIVERSARY

It is April 15 and I, the Editor of the Journal, cannot find the words to write an editorial for this 20th Anniversary Issue, an assignment given to me many months ago by our Publisher, Lou Le Jacq. I feel like the author I am badgering because he is late with the article he promised to send 6 months ago. Bill Roberts, in his tribute to me, states that I have written no editorials in my capacity as Editor. Actually, I wrote two, one for the Inaugural Issue in 1958 and one for the 10th Anniversary Issue in 1968. It is fitting that the third one is for this 20th Anniversary Issue.

When I became President of the American College of Cardiology in 1956, the Executive Committee of the Board of Trustees asked me to explore the need for a new journal on the heart to be sponsored by the College and then to find the best available publisher and editor. The need for such a journal for the clinical cardiologist was clearly established. After a long search, a publisher was found, the Yorke Medical Group, with which the College has maintained one of the closest, longest and most successful relations in medical publishing history. When it came to appointing an editor, the Board of Trustees made clear its choice—Simon Dack—a choice I could not readily accept because I had had only limited experience as Editor of the Transactions of the American College of Cardiology. But the Board insisted, and there I was in 1957, Editor-in-Chief of a fledgling journal with the task of organizing its Editorial Board and soliciting appropriate original articles. The first issue was published 1 year later. I hope the College's faith in me has been justified.

The College and its official Journal have come a long way together in the past 20 years in achieving their respective goals. I believe that we have both fulfilled our two most important functions: "to provide postgraduate education and a forum for dissemination of ideas and knowledge in cardiology." As Editor, my aim has been to provide such dissemination of new knowledge in a style and format that is understandable and appropriate for the clinician, the investigator and the educator. This requires a proper mix of clinical and experimental research papers and review articles that bring up to date what the clinician must know about cardiology. I have tried to encourage the expression of different points of view, the traditional as well as the nonconformist, and to be receptive to new ideas and disciplines in cardiology. As indicated in Gene Braunwald's editorial, with such a policy the Journal will continue to have an important impact on the practice of cardiology. In my continued tenure as Editor of the Journal, I hope that my determination and zeal to blend basic and clinical research with clinical practice, the new and innovative with the old and traditional, will not waiver and that the pages of the Journal will remain the place where "the basic scientist can talk to the clinician." The Journal must be a forum for the investigator as well as the practitioner and educator in cardiology. In this respect, both the College and the Publisher have allowed me complete independence to exercise my best judgment in the selection of manuscripts. I will continue to do so as fairly and responsibly as I can.

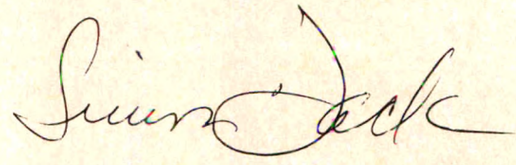
Bill Roberts quotes from one of my reports to the Editorial Board stating that " . . . the growth and success of the Journal are not due to the efforts of just one man." This is true. The Journal could not have succeeded without the help and support of the Associate Editors, my four capable and devoted Assistant Editors, the Editorial Consultants and all the reviewers for the Journal. Lou Le Jacq, our publisher, has been a true friend of the College and has always honored a request from me when I have told him it's for the good of the Journal. I have had complete support from every President, Officer and Trustee of the College, and from its Executive Director, Bill Nelligan, who has strength-

ened the close relations among the Editor, the Publisher and the College. And, of course, there is the ever-dedicated Ruth Ohman, my hardworking Executive Editor and "boss," who sees that I mind my P's and Q's and whose skilled professionalism makes my amateurish editing look polished.

The Publications Committee, chaired previously by John Ross and now by William Roberts, has been transformed into an efficient watchdog and oversight committee whose helpful recommendations have contributed to significant improvements in the Journal in the past 7 years. Both men have been of extraordinary help to me.

No busy practitioner, consultant and teacher in cardiology could have served successfully as Editor of this Journal without the understanding and support of his family. To my wife Jacqueline and to our children, Jerilyn and Leonard, my deep love and gratitude for your encouragement and support despite the many hours I have taken from you.

To my colleagues and the illustrious editors of other heart journals who have written the accompanying editorials and tributes for this occasion, I am grateful for your kind words, some of which I have considered editing and deleting. On second thought, I shall keep my blue pencil in the drawer and graciously accept your accolades. Thank you each and every one for contributing to this issue of the Journal. I pledge my continued dedication to serve the Journal as its Editor.



Simon Dack, MD, FACC
Editor-in-Chief
The American Journal of Cardiology

THE FIRST 20 YEARS OF

The American Journal of Cardiology

A Chronicle of the Golden Age of Cardiology

In the lives of individuals, groups, nations and areas of knowledge, indeed of entire societies, there are long barren periods when little progress appears to be taking place. Then suddenly a magic moment arrives, many diverse strands seem to come together and rapid forward movement takes place; that is, there is a true "golden age." It is ironic that the historic importance of such a period is rarely appreciated at the time of its occurrence; only after its passage is the true significance of the period of extraordinary progress recognized.

I submit that cardiology and cardiovascular science are experiencing a golden age at this very time and that *The American Journal of Cardiology,* under the devoted and wise leadership of its founding Editor, Simon Dack, has provided a most useful chronicle of this era during its first 20 years. In addition to this important function, by offering a forum not only for timely and provocative original articles, but also for short reports, preliminary communications and insightful speculative reviews, the Journal has actually contributed to the advances in cardiology by providing new insights and by identifying critical gaps of knowledge and areas of controversy.

Two Decades of Progress in Cardiology

It is an interesting exercise to compare the contents of the Journal during its 1st and 20th years of publication, an exercise that has given me new respect for just how much cardiology has progressed during this period. Compare, for example, the report by Kitchell et al.[1] in the first volume of the Journal, "Bilateral Internal Mammary Artery Ligation for Angina Pectoris," with two papers in the 40th volume, "Results of Coronary Bypass More Than Five Years After Operation in 434 Patients" by Lawrie et al.[2] and the report on experiences with medical treatment of the "Veterans Administration Cooperative Study of Surgery for Coronary Arterial Occlusive Disease."[3] In 1958 the surgical treatment of coronary artery disease was indirect; internal mammary artery ligation was based on a vague theory that had not been validated experimentally, and the evaluation of the efficacy of this procedure was subjective and anecdotal. In contrast, in 1978 the surgical treatment of severe angina pectoris by coronary bypass is direct and relatively safe; its effectiveness in relieving the pain of severe angina has been evaluated objectively[2] and, although the last word on its ability to prolong life is not yet in, rigorous statistical and epidemiologic methods are now being employed to examine the long-term results.[3]

Mitral valve disease: Let us examine the differences in the methods used in the diagnosis of mitral valve disease. In Volume 1, Luisada and Liu[4] reported on the use of the left atrial electrokymogram and the left atrial pressure pulse obtained by transthoracic puncture in the differentiation between mitral stenosis and regurgitation, a differentiation of critical importance at that time because mitral stenosis was operable and mitral regurgitation was not. Both of these techniques represented major advances over those previously available, but by today's standards they provide only indirect results and transthoracic puncture involved significant risk. In contrast, in Volume 40, Weyman et al.[5] report on the use of cross-sectional echocardiography in mitral valve disease. This noninvasive technique not only allows direct imaging and measurement of the size of the mitral valve orifice, but also permits recording of the rate of filling of the left ventricle. Also, in Volume 40 of the Journal is a clear demonstration of the effectiveness of echocardiography, not simply in detecting mitral regurgitation, but also in defining its etiology.[6]

Surgery for valve disease: What about the surgical treatment of valvular heart disease? In Volume 1, Charles P. Bailey et al.[7] described a procedure termed "neo-strophingic mobilization" that consisted of mobilizing the septal leaflet of the mitral valve and allowing it to function as a flap valve, a procedure said to be effective even when the valve was fibrotic. In the same volume, Paul Wood[8] summarized the high operative risks (20 percent) and the poor long-term results of operation for aortic stenosis as carried out 2 decades ago. In Volume 40, in contrast, are reports[9–11] of the greatly reduced operative mortality and excellent long-term follow-up resulting from prosthetic replacement of the aortic valve as well as the encouraging long-term function of both prosthetic valves and tissues valves.

Hypertensive heart failure: In Volume 1, Smirk and his associates,[12] in a remarkable; now classic paper, established the efficacy of treating hypertensive heart failure by reducing arterial pressure—using the then available ganglionic blocking agents. Twenty years later hypertensive heart failure is uncommonly encountered, and a principal clinical reason for treating hypertension is the primary prevention of coronary and cerebral arterial disease.[13] In 1958, although the incidence of acute rheumatic fever was decreasing, it was still considered to be of sufficient importance to warrant an entire Symposium in Volume 1. Rheumatic fever does not even appear in the index to Volume 40!

Congenital heart disease: In 1958 patients with congenital heart disease were still curiosities. Open heart surgery had just come on the scene, and the increased risk of correction of congenital anomalies in patients with serious pulmonary hypertension was becoming apparent. Thus, the report by Weiner et al.[14] on the use of the electrocardiogram in the detection of pulmonary hypertension in patients with ventricular septal defect was most timely. Observations on congenital heart disease occupied only a trivial fraction of the space in the Journal. Although the incidence of congenital heart disease has obviously not increased during the past 20 years, pediatric cardiology has made enormous strides. Indeed, the Journal now devotes a special section to pediatric cardiology in each issue. The spectacular developments of surgical treatment of congenital anomalies, particularly in infants, are reflected in a paper by Mair and McGoon[15] on the correction of atrioventricular canal during the first year of life, a procedure probably not even contemplated seriously 20 years ago.

Cardiac arrhythmias: There has been a revolution in our understanding and treatment of cardiac arrhythmias. For instance, in 1958, before discovery of transthoracic electrical countershock, the treatment of refractory ventricular tachycardia with intravenous quinidine was described and the hazards of the negative inotropic effects of this drug were pointed out.[16] Contrast this with the study[17] reported in Volume 40 in which the direct cardiac and vascular effects of intravenously administered quinidine were separated in five heart transplant recipients with anatomically denervated hearts, using metallic markers surgically implanted in the myocardial wall. It was shown that intravenous quinidine does not exert a potent negative inotropic effect and that its major hemodynamic action is most consistent with venodilatation. During the past 20 years the emphasis in the study of cardiac arrhythmias has turned from a description of the surface electrocardiogram to a physiologic analysis of the mechanism of arrhythmias, using programmed stimulation,[18,19] and to techniques such as sequential atrioventricular pacing.[20] Also, somewhat more effective antiarrhythmic agents are now available.[19,21]

Congestive heart failure: In 1958, in the treatment of refractory congestive heart failure, corticosteroids were utilized to augment diuresis[22]; prior to the introduction of the thiazide or loop diuretic agents, the then new diuretic drugs such as ethoxzolamide[23] and aminoisometradine[24] were described, substances that have now been long forgotten. Parenterally administered mercurial diuretic agents,[25] intramuscular digitoxin[26] and oral acetyl-digitoxin[27] received attention in Volume 1 as effective measures for treating heart failure. In contrast, in Volume 40 a persuasive case is made for the use of vasodilators in the treatment of chronic congestive heart failure[28–30] and of intraaortic balloon counterpulsation in certain acute cases.[31,32]

New approaches: Volume 40 abounds with many other concepts and techniques for the understanding, diagnosis and treatment of heart disease not even considered 20 years ago. Just a few among these are selective coronary arteriography; the use of myocardial technetium-99m pyrophosphate imaging in patients with myocardial infarction[33]; the many other applications of radionuclide angiography; transcatheter endocardial biopsy of the ventricles[34]; the use of ergonovine to provoke coronary spasm demonstrated by coronary arteriography[35]; the use of instantaneous force-velocity-length relations to define myocardial contractility in the intact human heart[36,37]; the use of ambulatory electrocardiograms to solve complex diagnostic puzzles[38]; intravenous diazoxide therapy in hypertensive crises[39]; demonstration of the reversibility of ultrastructural changes in the myocardium after cessation of prolonged intake of ethanol[40]; the use of beta adrenergic blockade for the treatment of three major disease states—hypertension, arrhythmias and angina[21,41]; and the concept of preserving ischemic myocardium after coronary occlusion.[42] Also, note the many forms of circulatory disease unrecognized in 1958, but part of the daily vocabulary of the cardiologist today and discussed in Volume 40. These include relatively common conditions such as mitral valve prolapse and idiopathic hypertrophic subaortic stenosis, as well as uncommon ones, such as Bartter's syndrome[43] and coronary arteritis due to the acute febrile mucocutaneous lymph node syndrome.[44]

A Change in Leadership

Although it is proper to celebrate these spectacular developments of the past 20 years, it is sobering to note that there has been a subtle, but nonetheless real change in the leadership of cardiology. Among the authors who contributed to Volume 1 of the Journal were such towering and colorful figures as Charles Bailey, Claude Beck, Richard Bing, Ignacio Chavez, Raymond Heim de Balsac, Bruno Kisch, Samuel Levine, Myron Prinzmetal, Wilhelm Raab, Sujoy Roy, David Scherf, Hans Selye, Horace Smirk, Demetrio Sodi Pallares and Paul Wood. These men, and other giants of cardiology, cardiac surgery and cardiovascular science such as Alfred Blalock, Herrmann Blumgart, Russell Brock, Andre Cournand, Charles Friedberg, Robert Gross, Hans Hecht, Louis Katz, Irvine Page, Helen Taussig,

Paul White and Carol Wiggers are either departed or have become less active.* During the past two decades cardiology has been deprived not only of outstanding scholars and clinicians, but also of a certain drive, force and style that have been so important in propelling the field forward. Who now has the breadth and historical perspective of the entire field to provide the type of overview offered by Ignazio Chavez[45] in the opening paper of the Inaugural Issue of the *Journal* entitled "Thirty Years' Progress in Cardiological Diagnosis"? Who now has the richness of clinical experience and the masterful ability to integrate this knowledge that allowed Samuel Levine[46] to discuss "Some Puzzling Points Concerning Angina Pectoris" in Volume 1? Who can now make the clinical-hemodynamic correlations as effectively as did Paul Wood[8] 20 years ago?

The Decades Ahead

We must not rest complacently as we contemplate the advances of the last two decades. We are in a golden age of cardiology, but I submit that this golden age has just begun. For example, in the past 20 years we have developed and learned how to use new drugs to lower arterial pressure in patients with hypertension and thereby to reduce the risks of a variety of complications, as well as to identify a number of curable forms of hypertension. However, we have not yet learned the cause of hypertension as it exists in the majority of patients and we have not yet learned how to motivate patients discovered to have hypertension to maintain effective therapy. We have learned how to diagnose complex congenital cardiovascular deformities by means of catheterization and angiography and to prolong the life of many infants by corrective and palliative operations, but we have not yet sorted out the genetic and fetal environmental abnormalities responsible for congenital heart disease, nor have we learned how to prevent these lesions. Similarly, during the last 20 years we have learned how to prevent recurrences of acute rheumatic fever and prevent the development of rheumatic heart disease, if the initial attack eluded preventive measures, and we have learned how to replace valves damaged from rheumatic fever. However, we have not yet learned how to diagnose streptococcal infection in all children, to treat all susceptible children long enough to prevent valve deformities, or how to prevent the development of valve deformities in patients who have never had an acute attack.

We have learned, by surgical procedures, to correct or bypass atherosclerotic obstructions in the major arteries of the body, including the coronary vascular bed, but we do not fully understand the fundamental mechanism responsible for atherosclerosis or how to prevent and treat it in an early stage. We have learned how to correct serious, often fatal cardiac arrhythmias by means of electric countershock and cardiac pacemakers, but we do not know how to treat the basic underlying conditions responsible for the arrhythmia. We have made some progress in identifying patients at risk for sudden death, but have not learned how to prevent this catastrophic event.

The celebration of this anniversary of *The American Journal of Cardiology* provides a marvelous opportunity to look back at the past 20 years but demands that we also look ahead. I am hopeful that the pages of the Journal in the next two decades will fill several of the gaps of knowledge I have mentioned. I anticipate that those of us fortunate enough to be around at the time of the Journal's 40th anniversary in 1998 will be as exhilarated by contemplating the differences between Volume 41 and 80 as we have every right to be when we examine the differences between Volumes 1 and 40.

Simon Dack has rendered outstanding and historic service to the entire field of cardiology as the midwife and parent of the Journal. He nurtured it carefully during its infancy and guided it into childhood and adolescence so that it is now a self-sustaining robust young adult. May he have the continued energy, drive and perspicacity to see it into maturity!

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* Dr. Richard J. Bing is the only author who contributed to both Volumes 1 and 40 of the Journal.

References

1. **Kitchell JR, Glover RP, Kyle RH:** Bilateral internal mammary artery ligation for angina pectoris. Am J Cardiol 1:46–50, 1958
2. **Lawrie GM, Morris GC, Howell JF, et al:** Results of coronary bypass more than 5 years after operation in 434 patients. Clinical, treadmill exercise and angiographic correlations. Am J Cardiol 40:665–672, 1977
3. **Detre K, Hultgren H, Takaro T:** Veterans Administration Cooperative Study of Surgery for Coronary Arterial Occlusive Disease. III. Methods and baseline characteristics, including experience with medical treatment. By the Veterans Administration Cooperative Group for the Study of Surgery for Coronary Arterial Occlusive Disease. Am J Cardiol 40:212–225, 1977
4. **Luisada AA, Liu CK:** Left atrial electrokymograms and pressure pulses in mitral valve disease. Am J Cardiol 1:68–80, 1958
5. **Weyman AE, Heger JJ, Kronik G, et al:** Mechanism of paradoxical early diastolic septal motion in patients with mitral stenosis. A

cross-sectional echocardiography study. Am J Cardiol 40:691–699, 1977
6. **Humphries WC, Hammer WJ, McDonough MT:** Echocardiographic equivalents of a flail mitral leaflet. Am J Cardiol 40:802–807, 1977
7. **Bailey CP, Hirose T, Morse DP:** Mitral stenosis—new concept of correction by rehinging of the septal leaflet (neo-strophingic mobilization). Am J Cardiol 1:81–102, 1958
8. **Wood P:** Aortic stenosis. Am J Cardiol 1:553–571, 1958
9. **Rubin JW, Moore HV, Hillson RF, et al:** Thirteen year experience with aortic valve replacement. Am J Cardiol 40:345–354, 1977
10. **Sarma R, Roschke EJ, Harrison EC, et al:** Clinical experience with the Smeloff-Cutter aortic valve prosthesis: an eight-year follow-up study. Am J Cardiol 40:338–344, 1977
11. **Fishbein MC, Gissen SA, Collins JJ, et al:** Pathologic findings after cardiac valve replacement with glutaraldehyde-fixed porcine valves. Am J Cardiol 40:331–337, 1977
12. **Smirk FH, Hamilton M, Doyle AE, et al:** The treatment of hypertensive heart failure and of hypertensive cardiac overload by blood pressure reduction. Am J Cardiol 1:143–153, 1958
13. **Borhani NO:** Primary prevention of coronary heart disease: a critique. Am J Cardiol 40:251–259, 1977
14. **Weiner SM, Levinson DC, Elek SR:** Ventricular septal defect and pulmonary hypertension. Electrocardiographic, spatial vectorcardiographic, and cardiac catheterization findings. Am J Cardiol 1:191–198, 1958
15. **Mair DD, McGoon DC:** Surgical correction of atrioventricular canal during the first year of life. Am J Cardiol 40:66–75, 1977
16. **Sigler LH:** Severe case of ventricular tachycardia. Treatment with intravenous quinidine. Am J Cardiol 1:637–639, 1958
17. **Mason JW, Winkle RA, Ingels NB, et al:** Hemodynamic effects of intravenously administered quinidine on the transplanted human heart. Am J Cardiol 40:99–104, 1977
18. **Josephson ME, Kastor JA:** Supraventricular tachycardia in Lown-Ganong-Levine syndrome: atrionodal versus intranodal reentry. Am J Cardiol 40:521–527, 1977
19. **Zipes DP, Gaum WE, Foster PR, et al:** Aprindine for treatment of supraventricular tachycardias. With particular application to Wolff-Parkinson-White syndrome. Am J Cardiol 40:586–596, 1977
20. **Hartzler GO, Maloney JD, Curtis JJ, et al:** Hemodynamic benefits of atrioventricular sequential pacing after cardiac surgery. Am J Cardiol 40:232–236, 1977
21. **Wellens HJJ, Bar FWHM, Lie KI, et al:** Effect of procainamide, propranolol and verapamil on mechanism of tachycardia in patients with chronic recurrent ventricular tachycardia. Am J Cardiol 40: 579–585, 1977
22. **Riemer AD:** Application of the newer corticosteroids to augment diuresis in congestive heart failure. Am J Cardiol 1:488–496, 1958
23. **Moyer JH, Ford RV:** Laboratory and clinical observations on ethoxzolamide (Cardrase) as a diuretic agent. Am J Cardiol 1: 497–504, 1958
24. **Callen IR:** The effectiveness of Rolicton, a new oral diuretic, in severe cardiac failure. Am J Cardiol 1:511–513, 1958
25. **MacHaffie RA, Humoller FL, Walsh JR:** A study of the effectiveness of mercurial diuretics in treatment of cardiac decompensation. Am J Cardiol 1:505–510, 1958
26. **DeFrancis NA, Klements J, Gordon A:** Clinical evaluation of intramuscular digitoxin in the management of congestive heart failure. Am J Cardiol 1:723–725, 1958
27. **Vacca JB, Schuster JM, Knight WA:** Clinical evaluation of acetyl-digitoxin. Am J Cardiol 1:717–722, 1958
28. **Hardarson T, Henning H, O'Rourke RA:** Prolonged salutary effects of isosorbide dinitrate and nitroglycerin ointment on regional left ventricular function. Am J Cardiol 40:90–98, 1977
29. **Aronow WS, Greenfield RS, Alimadadian H, et al:** Effect of the vasodilator trimazosin versus placebo on exercise performance in chronic left ventricular failure. Am J Cardiol 40:789–793, 1977
30. **Massie B, Chatterjee K, Werner J, et al:** Hemodynamic advantage of combined administration of hydralazine orally and nitrates nonparenterally in the vasodilator therapy of chronic heart failure. Am J Cardiol 40:794–801, 1977
31. **Lefemine AA, Kosowsky B, Madoff I, et al:** Results and complications of intraaortic balloon pumping in surgical and medical patients. Am J Cardiol 40:416–420, 1977
32. **Hagemeijer F, Laird JD, Haalebos MP, et al:** Effectiveness of intraaortic balloon pumping without cardiac surgery for patients with severe heart failure secondary to a recent myocardial infarction. Am J Cardiol 40:951–956, 1977
33. **McGowan RL, Martin ND, Zaret BL, et al:** Diagnostic accuracy of noninvasive myocardial imaging for coronary artery disease: an electrocardiographic and angiographic correlation. Am J Cardiol 40:6–10, 1977
34. **Kawai C, Kitaura Y:** New endomyocardial biopsy catheter for the left ventricle. Am J Cardiol 40:63–65, 1977
35. **Schroeder JS, Bolen JL, Quint RA, et al:** Provocation of coronary spasm with ergonovine maleate. A new test with results in 57 patients undergoing coronary arteriography. Am J Cardiol 40: 487–491, 1977
36. **Weber KT, Janicki JS:** Instantaneous force-velocity-length relations: experimental findings and clinical correlates. Am J Cardiol 40:740–747, 1977
37. **Nichols WW, Conti CR, Pepine CJ:** Instantaneous force-velocity-length relations in the intact human heart. Am J Cardiol 40: 745–761, 1977
38. **Reiffel JA, Bigger JT, Cramer M, et al:** Ability of Holter electrocardiographic recording and atrial stimulation to detect sinus nodal dysfunction in symptomatic and asymptomatic patients with sinus bradycardia. Am J Cardiol 40:189–194, 1977
39. **McDonald WJ, Smith G, Woods JW, et al:** Intravenous diazoxide therapy in hypertensive crisis. Am J Cardiol 40:409–415, 1977
40. **Weishaar R, Sarma JSM, Maruyama Y, et al:** Reversibility of mitochondrial and contractile changes in the myocardium after cessation of prolonged ethanol intake. Am J Cardiol 40:556–562, 1977
41. **Zweifler A, Ester M:** Blood pressure, renin activity and heart rate changes during propranol therapy of hypertension. Am J Cardiol 40:105–110, 1977
42. **Kloner RA, Fishbein MC, Maclean D, et al:** Effect of hyaluronidase during the early phase of acute myocardial ischemia: an ultrastructural and morphometric analysis. Am J Cardiol 40:43–49, 1977
43. **Potts JL, Dalakos TG, Streeten DHP, et al:** Cardiomyopathy in an adult with Bartter's syndrome and hypokalemia. Hemodynamic, angiographic and metabolic studies. Am J Cardiol 40:995–999, 1977
44. **Kitamura S, Kawashima Y, Kawachi K, et al:** Left ventricular function in patients with coronary arteritis due to acute febrile mucocutaneous lymph node syndrome or related diseases. Am J Cardiol 40:156–164, 1977
45. **Chavez I:** Thirty years' progress in cardiological diagnosis. Am J Cardiol 1:3–18, 1958
46. **Levine SA:** Some puzzling points concerning angina pectoris. Am J Cardiol 1:19–25, 1958

A FAMILY PARTY

We were swapping editorial stories, Simon Dack and I, outside the Las Vegas Convention Center when the American College of Cardiology was meeting there in 1977. I was a comparative novice, he an old hand with the answer for everything. He'd lived through all the travails, survived all the editorial crises and denied any secret skills. The Journal, he said, runs itself when you pick the right people to help you, the right publishers, administrative staff and the best medical communicators in the country. His editorial committee was meeting in the next few minutes, and wouldn't I join them in Room D. Room D that day was like a family party, all Simon's best communicators seated around a long oblong table, while he, communicator-in-chief, took his place at the head, mounted on a low dais like a conductor about to create music. He reminded me of a Stokowski rehearsal I once slipped into: the maestro surrounded by the country's finest instrumentalists, drawing out their individual talents and bringing them all together with his particular type of magic. Simon in Las Vegas called on this one and that to give a little solo—the theme was Editorials—now agreeing, now arguing or countersuggesting but all the time clearly delighted with the whole arrangement. Everyone had his say, and if someone didn't speak up, Simon pointed, "What about it, Bill? Are you going to let him get away with that!?"

He wanted to know about British Heart Journal policy, why we did this or that, the future of SI units, should there be referees, how many, and should they be paid, each point setting off fresh talk and sometimes little revolutions around the table. Then a few lively sociable exchanges with the publisher, a final brief round of compliments and criticisms, and the session ended, Simon asserting to the end his aggressive editorial independence and I feeling very much at home.

The Pulitzer prizes are awarded for poetry, music, fiction, drama and history; if I had my way, I'd include one for medical editing . . . and award it to Simon Dack.

Walter Somerville

Walter Somerville, MD, FACC
Editor
British Heart Journal

NOTES FROM A COLLEAGUE

This issue, paying tribute to Simon Dack, commemorates the 20 years in which he has served as Editor of *The American Journal of Cardiology*. It coincides with publication of the first issue of *Circulation*, of which I have assumed responsibility as Editor.

As a novice editor, I look with some awe and sheer amazement at the stamina of this man and his accomplishments with the Journal over the past 20 years. The eminence that *Circulation* has achieved during its 28 years of publication was reached through the efforts of a number of editors who devoted themselves to that journal. Simon Dack, in contrast, single-handedly took a fledgling journal and developed it into one of the premier journals in the cardiologic field. From a beginning in which only a handful of subscribers used the Journal, he has built *The American Journal of Cardiology* so that it now reaches more than 23,000 subscribers every month.

Members of the American College of Cardiology are appropriately proud of their official organ. It serves as an important educational tool and publishes articles reflecting significant clinical research, the development of new methods, clinical observations, results of therapy, pertinent experimental studies and reviews on timely subjects. The quality of its articles has increasingly improved over the years and reflects the clinical skills that Simon Dack himself possesses.

Simon Dack has an encyclopedic knowledge of the scientific literature. He has been an indefatigable worker, dedicated to the continuing improvement of *The American Journal of Cardiology*. He has remained respected, admired and well liked after 20 years as Editor. Editors, like medical school deans, rarely remain in favor for months, let alone years. To be held in affection and admiration after 20 years testifies to the fairness and objectivity that he has brought to the decisions made as Editor in his dealings with authors and readers alike. As a result of his efforts, *The American Journal of Cardiology* is now one of the world's outstanding medical journals.

The Associate Editors of *Circulation* and I are proud to join in this tribute to Simon Dack, and to wish him further success as Editor of *The American Journal of Cardiology*.

Elliot Rapaport

Elliot Rapaport, MD, FACC
Editor
Circulation

SI DACK, MD

Simon Dack has made important contributions to education and advancements in knowledge in cardiology during his 20 years as Editor of *The American Journal of Cardiology*. The thousands of papers published have supplied an outlet for information from authors to readers. The Journal has effectively represented all aspects of cardiology during these years and has provided a continuum of information on advances in cardiology with ultimate benefit to the patient. The Journal has grown in circulation and importance during the past 20 years under the mature and effective guidance of Si Dack.

To appreciate *The American Journal of Cardiology* fully, it is necessary to know the Editor-in-Chief. Si Dack is a fair man. He is honest, and he readily and consistently recognizes those who have been responsible for new ideas and advances in cardiology. He is not prejudiced in the selection of papers for publication, as is evident from a review of any volume of his Journal. He participates in clinical cardiology himself. He is a cardiologist who cares for patients and who is able to evaluate personally what he publishes. He therefore knows what is happening in private offices and in the hospitals of his city and country. Si teaches, lectures and participates actively in cardiology, and he knows the influence his Journal has in the entire field of cardiology. Si is aware of the activities in cardiology, long before manuscripts on the respective subjects reach him. He is fully aware of his responsibilities as Editor of the Journal, and he is highly respected in cardiology and in the field of medical publication.

Si, through *The American Journal of Cardiology*, has made important contributions to the American College of Cardiology. *The American Journal of Cardiology* is the official journal of the American College of Cardiology. For 1 year Si was both President of the College and Editor of the Journal. While maintaining his loyalties and responsibilities to the Journal, he has not allowed any conflict of interest to impair his responsibilities to its sponsor, the American College of Cardiology. Si's personality, fairness and unselfish interests have made him an excellent editor. He has managed this difficult position gracefully and without conflict of interest or controversy. May he continue to discharge this responsibility for many years to come and in good health, with good luck and great happiness. The publishers owe a debt of gratitude to their Editor-in-Chief.

Many thanks, Si, from all of us who read your Journal regularly.

George Burch, MD, FACC
Editor
American Heart Journal

CARDIOLOGY FOR THE CLINICIAN: SIMON DACK'S EDITORIAL PERSPECTIVE

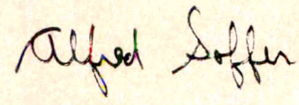
An editor's philosophy and interests are reflected most clearly in the journal departments that are structured by his invitation. The Editor of *The American Journal of Cardiology* is a superb investigator, teacher and clinician. All of these facets of his career are mirrored in the pages of the periodical he has directed so ably for two decades. However, by perusing special sections such as "Diagnostic Shelf," "Reports on Therapy" and "Reviews," one learns of Simon Dack's particular concern for the practitioner of cardiology.

The enormous increase in biomedical research in the past 20 years has resulted in a continuing torrent of reports of basic investigational nature. *The American Journal of Cardiology* accepts the responsibility to serve the needs of this segment of the cardiovascular community by providing stringent peer review procedures that lead to eventual publication of the finest original investigations. A distinguished Editorial Board and authoritative out-of-office consultants screen each manuscript for validity and significance. Their skills are evidenced by the number of historic contributions in cardiology that have appeared in *The American Journal of Cardiology*. Physiologists, cardiovascular pathologists and laboratory scientists have been afforded a national forum in its pages. However, in 1958 Simon Dack perceived that large numbers of physicians who treated patients with cardiovascular diseases believed that relatively few articles in specialty journals had clinical relevance. He feared disenfranchisement of practicing specialists who required practical guidance for daily needs. Aware of the responsibility to assist both practitioner and investigator, Simon Dack used his creative energies to mold a journal that serves both readerships.

Dramatic changes have occurred in medical education in the past 20 years. An increasing number of state governments have notified the medical profession that proof of continuing education will be a requirement for relicensure, and some specialty societies have established similar requirements for membership. As a result, there has been a preoccupation with mandatory attendance at postgraduate courses and an emphasis upon self-assessment workbooks and a host of other innovations. Important as some of these contributions may have been, we were threatened with neglect of medical periodicals. Strong leadership was required to remind the medical community of the invaluable role the society journal plays in the continuing education of the graduate physician. It was necessary for editors to counter the accusation that specialty journals serve exclusively the gratifications of the investigator. Because he is a master clinician it is not surprising that Simon Dack responded to the needs of the practitioner as well as those of the full-time faculty member. Proof that his editorial creation fills current needs is evidenced by the striking growth in the number of subscriptions. The physician who treats myocardial infarction, congestive heart failure or congenital heart disease, whether he be in a rural or urban community, finds communications of direct interest to him in each issue. Bedside clinicians in Los Angeles, Syracuse, Montreal, Rome and Tokyo know that Simon Dack is aware of their concerns. House officers and medical students appreciate the assistance that the Journal provides for them in their hospital rounds.

What of Simon Dack's working habits? His phenomenal memory brings delight to his Associate Editors and Senior Assistant Editors. Woe betide the hapless author who attempts to submit a "retread" under the guise of current investigation. Si may point out to his colleagues that " . . . this author submitted essentially the same work 3 years ago. The original manuscript described a few less patients and it had a different title but it is still an unacceptable paper!" His intimate acquaintance with recent and current medical reports makes it possible for him to sort out the repetitious from the fresh, the pedestrian from the original, and thus he saves the reader the wasteful task of reading the insignificant and the redundant.

As the official journal of a splendid specialty professional society, *The American Journal of Cardiology* mirrors the aspirations of that society. One of the most skilled cardiologists of our era has brought to that periodical his enthusiasm for teaching and the discriminating taste of someone who has unique talents in the art and science of cardiovascular medicine. We are indebted to him for his skillful and dedicated service and look forward to the years ahead when we shall continue to have the privilege of being students in his editorial classroom.



Alfred Soffer, MD, FACC
Editor
Chest

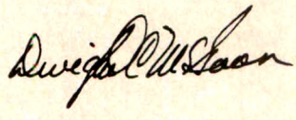
A PERSONAL TRIBUTE

Simon Dack is admired for his precise, informal, incisive and highly successful leadership of the Journal that he has nurtured to the front rank. It was therefore with reluctance that I felt compelled recently to resign as an editorial consultant to his Journal because of my own status as a neophyte editor. My personal esteem for this paragon among editors is reflected in my recent letter to him:

"... I can assure you that I have particularly enjoyed serving as a consultant to you and your staff, and that I am most sincerely impressed at the expert, innovative and industrious guidance you have given *The American Journal of Cardiology* through your years as its Editor. If I could begin to compare in my new responsibility with the successes which you have achieved, I would be extremely gratified. In that connection, I might also ask permission to seek your advice and counsel from time to time in the future as the occasion may arise. I would value it most highly."

Needless to say, this dedicated servant of our profession freely offered me his assistance, as he has through the years to investigators, authors, reviewers, students and patients.

It gives us all confidence to know that we can continue to call upon the wisdom and experience of this great leader.



Dwight C. McGoon, MD, FACC
Editor
The Journal of Thoracic and Cardiovascular Surgery

SIMON DACK AND

The American Journal of Cardiology

The American Journal of Cardiology first appeared in January 1958, and this year represents its 20th birthday. During these two decades, the Journal has grown each year in number of readers, subscribers and manuscripts submitted, so that at present it is the most widely read cardiology journal (three independent surveys) and has the largest number of subscribers (over 23,000) of any cardiology journal in the world. In addition, it is the fastest growing medical journal in the United States. The number of manuscripts submitted to the Journal in 1977 was 1,022 or nearly 20 a week. This number represents a 100 percent increase in number of manuscripts submitted since 1968 and a 50 percent increase in the past 5 years alone. The number of pages of the Journal allocated to the accepted manuscripts also has increased yearly so that in 1977 over 2,100 nonadvertising pages were published. The Journal is, by a considerable margin, the most popular of the cardiology journals among advertisers, and this advertising growth has allowed publication of more pages of manuscripts. In recent years the Journal has published 13 and 14 issues annually, rather than 12, and these additional issues are made possible because of the strong advertising support.

What is responsible for this phenomenal growth of *The American Journal of Cardiology* during these past 20 years? One factor is the *growth in the number of potential and real subscribers* during this period. The number of physicians, hospitals, medical schools, medical libraries and large medical clinics has increased enormously in recent years. Another factor is the *growth in membership and prominence of the American College of Cardiology,* and every member of the College automatically is a subscriber to the Journal. Another factor is *strong support and cooperation from the publisher and his staff.* None of these three factors, however, provides an adequate explanation for the rapid growth of the Journal. Many medical journals (and there are now more than 140,000 bioscience journals published worldwide each year) during this period actually decreased in numbers of readers, subscribers and manuscripts submitted. More than 60 percent of the subscribers to the Journal are non-College members, and some first-rate medical publishers are burdened with second- and third-rate publications because of medical factors they do not control.

The major factor responsible for the rise of *The American Journal of Cardiology* to its leadership position within a 20 year period is the *high quality of the articles* published in it. What factors are responsible for this high quality? First, *first-rate articles are submitted* to the Journal for consideration for publication. To publish first-rate articles, first-rate manuscripts must be received. At present, of every 100 manuscripts submitted, about 22 are accepted. (The acceptance rate, incidentally, has remained at this level for some years, despite about a 10 percent yearly increase in number of manuscripts submitted, only because the number of pages published has increased about 10 percent annually.) Another factor responsible for the high quality of manuscripts published is the *excellence of the reviews of the papers* by members of the Editorial Board and by outside editorial consultants, and appropriate revisions of the submitted manuscripts by the authors. Each of the 75 Editorial Board members reviews about 12 manuscripts yearly. All manuscripts, however, receive two reviews, many three reviews, so that outside consultant reviewing is essential. Another factor is the *superb assistance of the Assistant Editors.* Another is the excellent work of Ruth Ohman, the Journal's Executive Editor, her assistants and her predecessors. Another is *helpful suggestions for improvement of the Journal by members of the Editorial Board, the Publications Committee of the College and others.* And, finally, the *guidance provided by a devoted, informed, hard-working, thorough, fair, independent, confident, open-minded, efficient, realistic, unselfish, creative, modest, humble, personable, genuine and relaxed Editor-in-Chief* has been crucial.

Who is this Simon Dack who possesses such an array of attributes? Si Dack is "a native New Yorker," born on April 19, 1908, and he has lived in "the city" ever since. He was graduated from the College of the City of New York in 1928 and from New York Medical College in 1932. He trained at the Mount Sinai Hospital in New York and has been a cardiologist on its staff ever since. After completion of training, he went into private practice, initially with Dr. Arthur M. Master, and he has been a sought-after consultant cardiologist ever since. He is now Consultant Cardiologist and Emeritus Clinical Professor of Medicine at the Mount Sinai School of Medicine and for several years was Chief of its Division

of Cardiology. Since January 1958, he has been Editor-in-Chief of *The American Journal of Cardiology*, and during these past 20 years 257 issues of the Journal have been imprinted with his unmistakable stamp. Si Dack in his modest way emphasizes that "the growth and success of the Journal are not due to the efforts of just one man," that is, the Editor-in-Chief. Fortunately, however, as Editor-in-Chief for all these years, Si Dack has been more than "just one man." Let us look into those attributes of his that make him today cardiology's most renowned editor.

Well informed professionally. Si Dack lives daily in the real world of cardiology. He takes care of patients with heart disease. He is attuned to what the practicing cardiologist needs to know. His intimate connection with a prominent medical school and hospital also keeps him attuned to the needs of the academic cardiologist. For several decades he has been a student of cardiologic writings, and he detects quickly what is good and who is good. Indeed, this wise editor keeps well ahead of the general status of knowledge.

Hardworking, efficient, organized, thorough. Si Dack spends 25 to 30 hours a week on the Journal. He reviews personally every manuscript before and after acceptance as well as the final page proofs. There is a general view that the Editor-in-Chief simply acts as the final judge of which manuscripts are accepted for publication. Certainly, Si Dack plays an active role in this selection process, but his "work really just begins after the manuscript is accepted." While the classical music plays in the background, each accepted manuscript receives his personal editorial touch, and he edits for the readers rather than for the authors (or himself). He tries to give the readers what they need and what they want. His weekly meetings with his Assistant Editors are examples of efficient and effective organization.

Fair, ethical. Si Dack favors no particular investigator, group or medical center, and he avoids no issue or idea. He evaluates not only a review of a manuscript but also the reviewer, because reviewing a manuscript occasionally brings out the worst in people. Therefore, Si Dack does not take the opinions of his reviewers as necessarily the correct view, and he will accept a manuscript despite two negative reviews if he believes that the reviewers were unfair or prejudiced against the author. Another example of his fairness was his resignation some years ago as Chairman of the Publications Committee of the College. He felt that an editor and his policies and activities should be overseen by an independent body.

Independent, confident. In these days of enormous pressures to publish to survive in the academic arena, Si Dack does not succumb to pressures to publish manuscripts which are not up to high standards. Although he derives no pleasure from such chores, Si Dack has no hesitation in refusing a manuscript submitted by one of his friends or even by one of the Editorial Board members who, let's say, just reviewed superbly three manuscripts for him in the last 3 weeks. It is also not easy for an editor to request an editorial or a review from someone and then have to refuse to publish it because the standards are not up to par. Again, Si Dack with self-assurance makes these decisions correctly, for his basis for all decisions is simply, "What is best for the Journal?" Si Dack also is not burdened at present by responsibilities for directing a large Department of Medicine or Division of Cardiology from which considerable pressure might be felt to favor members of his own unit.

Open-minded. Si Dack would rather listen than talk. He is open to suggestions that might improve the Journal. An example of this openness is the manner in which he conducts the annual meeting of his Editorial Board. During the first 15 minutes or so of the meeting, both Si and the Publisher give status reports on the Journal. Thereafter, for the next 45 to 60 minutes, the floor is open for discussion. "What am I doing wrong?" he asks. He actively seeks suggestions that might improve the Journal. He also listens to suggestions from the Publications Committee of the College. Under John Ross's leadership of this Committee from 1971 to 1977, several procedures for standardizing the operations of the Journal were formulated. These included (1) limiting terms of the Editorial Board members; (2) requiring written reviews by at least two reviewers of all manuscripts, including editorials, symposia and reviews as well as original articles; (3) requiring approval of Editorial Board members by the Publications Committee; and (4) making concerted efforts to diminish the lag time between acceptance of a manuscript and its publication. (This time period now is under 6 months.)

Modest, humble, personable, unselfish, relaxed. Si Dack is a warm, straight, unpretentious, genuine and relaxed man. Because the Journal runs so smoothly and because he keeps such a low profile, it is easy to take him for granted. He reminds me of the duck who floats so calmly on the surface of the water and the rapidly moving legs beneath are not visible. A paper by Si Dack infrequently appears in the Journal although he has about 165 publications to his credit. Excluding abstracts, he has published about 10 articles in the Journal in 20 years and never an editorial. Si Dack serves as a conduit through which others may glow, and he polishes all our manuscripts. Si Dack's style reminds me of an anecdote told about Saxe Commins, the great editor at Random House for 25 years, who finely tuned the works of Eugene O'Neill, William Faulkner and others. Once, when Saxe Commins was at a cocktail party and standing by himself in a corner, a lady bustled up to him and asked, "Why are you in a corner? Are you a writer?" "No," he said. "Then what do you do," she wanted to know, and Commins replied: "I'm in the cleaning and repairing business" (Commins D: What Is An Editor? Saxe Commins At Work, University of Chicago Press, 1978, 232 pages). His modesty was recently emphasized to me at an elegant dinner in March 1978 given by Lou Le Jacq, the publisher, in honor of Si Dack on this 20th anniversary. The table was long, with single seats at both ends. Si insisted that the outgoing and incoming

presidents of the College sit at these head chairs, and he joined the others of us along the sides. His modesty and humility, however, do not diminish the underlying vigorous, strong, confident leadership with which Si Dack directs the Journal.

Si Dack obviously is well aware of the enormous responsibility of an editor of a major journal today, and he does not abuse or misuse this power. Editors, in essence, determine what is news and, therefore, they govern the academic fates of many of us in the world of investigative medicine. Although nearly all medical writers can get their works published somewhere, only those reports that appear in the prominent medical journals, for practical purposes, cause significant shifts in the practice of medicine. Thus, the Editors-in-Chief of the major journals serve, to some extent, as "superbosses" through which all medical ideas and medical careers must travel. Si Dack handles this "superboss" role with quiet excellence. John Selden, the acknowledged master of the Antiquarian Society, said it best, "Those who govern the most make the least noise."

Devoted. Si Dack's devotion extends far beyond his fierce loyalty to the College and to its official Journal. He is a devoted family man, and his devotion to his wife Jackie and their two children, Leonard and Jerilyn, is wonderful to behold. All of us are fortunate that his family has willingly shared Simon's time with us through these 20 years, and we extend our deep-felt thanks to them.

In summary, the Publications Committee of the College is proud of Si Dack's editorship and unanimously in March 1978 recommended to the Executive Committee of the College that his contract as Editor-in-Chief of the Journal be renewed for another 5 year term beginning July 1, 1978. Fortunately, for cardiology in general and *The American Journal of Cardiology* in particular, Si Dack accepted. Thus, this modest man will surpass the reign of other recent 20 years giants—Sir Theodore Fox at the *Lancet* from 1945 to 1965, Hugh Clegg at the *British Medical Journal* from 1947 to 1965, and Joseph Garland at *The New England Journal of Medicine* from 1947 to 1967—and he will follow in longevity a 25 year giant, Alexander B. Gutman, at *The American Journal of Medicine* from 1946 to 1971. Editorships of these time spans now are rare, but with Si Dack we have a successful pilot and we know that the ship will move steadily onward to its proper destination.

William C. Roberts

William C. Roberts, MD, FACC
Chairman, Publications Committee
The American College of Cardiology

SIMON DACK, MD—EDITOR-IN-CHIEF

Reflections of the Senior Assistant Editors

With gratification, we have seen *The American Journal of Cardiology* start as a fledgling and, in the 20 years since its birth, assume a preeminent internationally recognized position as a major resource and force in the education and training of cardiologists. Although many people are associated with this success, it is in largest measure attributable to the Journal's founder and sole Editor-in-Chief, Simon Dack.

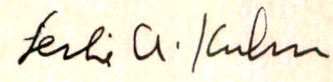
Elsewhere in this issue, Dr. Eugene Braunwald chronicles the enormous advances in cardiology during the 20 years of the Journal's existence, advances that the Journal has presented to the profession in a variety of ways but always, at the Editor's insistence, in a concise, readable format. The wide range of material has included original clinical studies, basic scientific and clinical research, symposia, seminars and reviews, descriptions of new methods, letters to the Editor, reports of therapy and case reports. To supervise the Journal team, to recognize and even anticipate significant advances in a rapidly changing field, to separate the important from the trivial and to eliminate the false, to meet deadlines and to perform the many onerous tasks associated with presenting each month an attractive publication with impeccable journalistic and professional standards requires a special person. We have always known Simon Dack to be that special individual.

These unique personal characteristics of Simon Dack the man make Simon Dack the Editor a recognized success. He combines an enormous capacity for work with an equally enormous dedication to the Journal in all details: from selection of articles to an insistence on the highest technical quality in production of the Journal. At an age when many who have achieved his eminence may reason that they have "paid their dues" to their career and slacken their pace of production in pursuit of more comfortable pleasures, Simon continues to work with an intensity and capacity that have remained undiminished over the years. He is aided—in no small measure—in this pursuit of excellence by the attitude and support of his lovely wife, Jackie (who, incidentally, chose the color of the Journal's original cover) and his two outstanding children. He has achieved these accomplishments despite great demands on his time from his teaching activities, clinical investigations and a busy practice as a much-sought after cardiologic consultant.

A close look at Simon's background shows that, like the Journal, he has grown up with cardiology as an investigator, teacher, practitioner and consultant. This experience gives him that great intuitive ability to judge and assess with amazing accuracy the intrinsic worth of an article or an idea, to analyze and predict advances in the field and to present them in an understandable, informative manner. His daily involvement with patient care in the most difficult areas in cardiology equips him to see the Journal as a practicing cardiologist might, to pose the same questions and seek the same answers as our knowledgeable readership. He is not separate and apart from the practicing cardiologists trying to help their patient—he is one of them. But he is more, because of his research background and enormous experience in teaching young cardiologists and in treating patients.

As cardiology became more complex over the years, editing the Journal also became more difficult. But Simon never hesitates to secure the best informed opinions from experts in the field before accepting or rejecting an article for publication. He does not impose his personal opinion if more knowledgeable experts are available. He scrupulously avoids "favoritism" or partiality because of the prestige of the author or his institution. Similarly, the lack of such prestige has never prevented acceptance of a worthwhile contribution. Simon's sole philosophy has been to publish the best, without regard to friendship or to other pressures. In a word, Simon has integrity. And of all his admirable characteristics that propelled the Journal to its present position, this is probably the most important.

For the Senior Assistant Editors, the appointment to work closely with Simon during these many years has been an unusual continued precious learning experience of the highest and most exciting intellectual calibre. We are looking forward to the next 20!



For the Senior Assistant Editors
Leslie A. Kuhn, MD, FACC

Ira J. Gelb, MD, FACC
Raymond Harris, MD, FACC
Melvin Kahn, MD, FACC

TO OUR EDITOR

It seems to me that medicine, medical writing and medical publishing are analogous. They share the same disciplines, opportunities and pitfalls.

The physician deals with that multifaceted, mysterious organism called man—making that work most effectively is his goal. Medical authors try to express in effective terms the results of their complex intellectual and practical experiences. Medical publishers try to provide the effective vehicle for transmitting that knowledge. The thread common to these activities is effectiveness in the face of an enormous mass of complexities and pitfalls.

It is our privilege to have provided Dr. Simon Dack an effective medium for the dissemination of outstanding editorial work. Final selection of editorial content, the lifeblood of the Journal, is his responsibility. His talent in determining that selection is its heart.

The tributes to him and the Journal in this issue speak well of the contributions that this gifted Editor has made during these 20 years. I can only add the thought that Simon Dack is unique because in him we find melded the most elusive of attributes—dedication, sensitivity, humility and common sense.

An Irish toast to you, Simon, "May the wind be always at your back, may the roads rise to meet you and may God hold you in the palm of His hand."

On to the next 20 years!

Louis F. Le Jacq

Louis F. Le Jacq
Publisher
The American Journal of Cardiology

FUTURA PUBLISHING COMPANY

as a medical publisher with a special interest in cardiology extends congratulations to The American Journal of Cardiology on the occasion of its 20th Anniversary. It is with pride that we take this opportunity to present a listing of our titles in cardiology.

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Bolooki: **CLINICAL APPLICATION OF INTRA-AORTIC BALLOON PUMP**
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Wolf and Eliot: **PRACTICAL MANAGEMENT OF HYPERTENSION**
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P A C E

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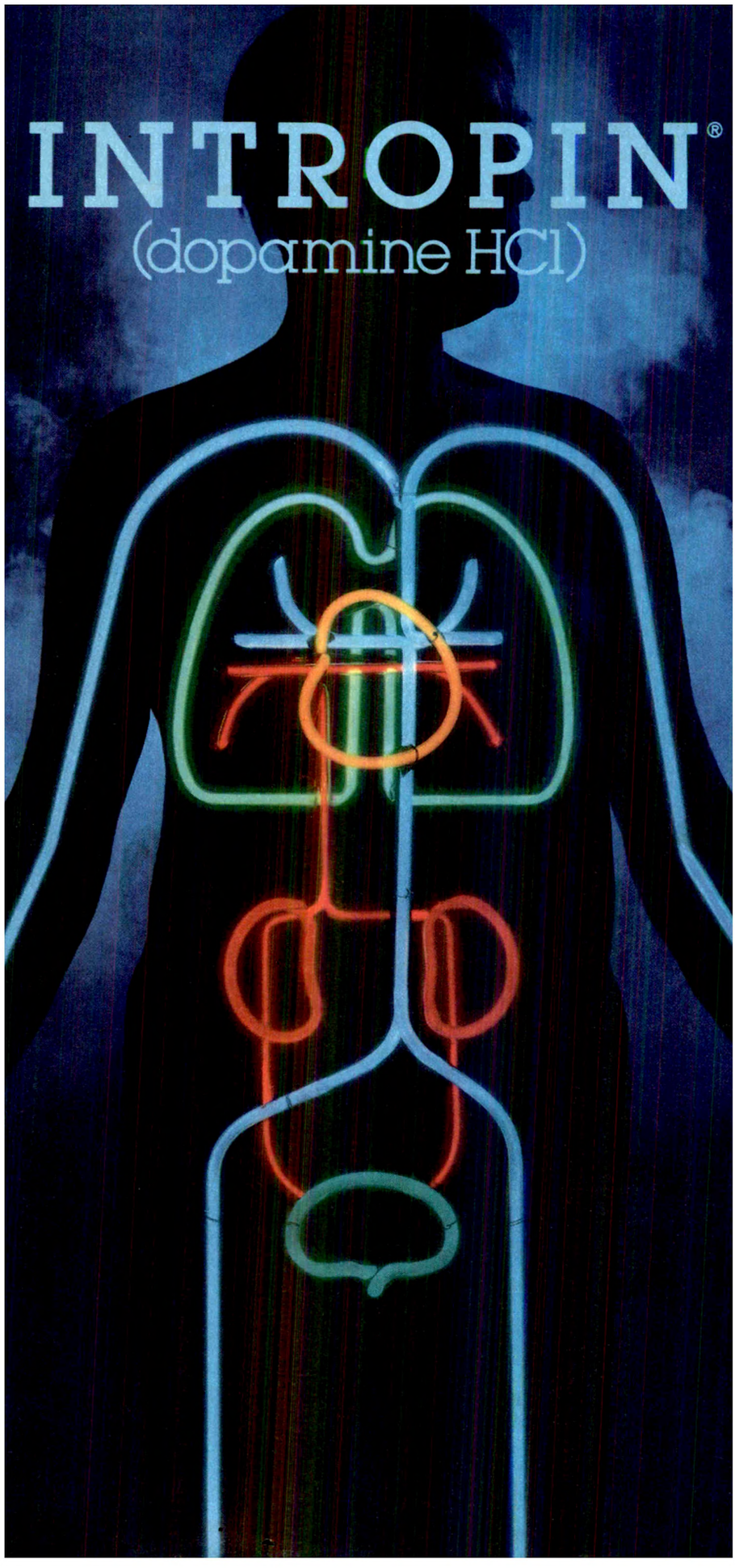
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In the shock syndrome:

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In the shock syndrome, perfusion pressure usually does not meet the metabolic needs of the vital organs. When volume replacement fails to reverse this process, additional therapy must be initiated to increase cardiac output and blood pressure and to increase blood flow to vital organs.

Intropin (dopamine HCl) is the only drug that both increases cardiac output and blood pressure while specifically redirecting the blood flow.

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The unique ability of Intropin to act on the "dopaminergic" receptors in the mesenteric and renal vasculature causes vasodilation in these beds and leads to increased renal blood flow, glomerular filtration rate and urine output. At low dose levels (less than 5 mcg/kg/min), when cardiac stimulation is not usually observed, these increases are independent of increased cardiac output.

In comparison, norepinephrine causes vasoconstriction in these beds, further compromising vital organ function.[1] Isoproterenol causes generalized systemic vasodilation (thereby requiring greater cardiac output to increase vital organ perfusion) and does not increase the renal fraction of the increased cardiac output.[2]

Increases cardiac output

At higher doses (above 5 mcg/kg/min), Intropin begins to increase myocardial contractility, stroke volume and cardiac output by direct positive inotropic effect while maintaining much of the unique dopaminergic effect. In certain patients such as refractory congestive failure patients, the increase in cardiac output may be seen at doses of less than 5 mcg/kg/min.

Norepinephrine, on the other hand, has a similar inotropic effect, but the expected increase in cardiac output is often diminished due to the increased systemic vascular resistance (afterload) resulting from norepinephrine's alpha adrenergic activity. Isoproterenol increases cardiac output in part through a chronotropic effect.[3] Its use results in a greater increase in myocardial oxygen consumption than does the inotropic effect of Intropin. It also results in a greater potential for arrhythmias.[3] The increased cardiac output obtained with isoproterenol is delivered to the total systemic vasculature due to general vasodilation while the selective vasodilation of Intropin directs more blood supply to the areas in need of vital perfusion.

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Intropin doses of over 20 mcg/kg/min will usually result in an alpha adrenergic (vasoconstriction) response in the peripheral vasculature. This usually raises the pressure and also redirects blood flow through the vasodilated vasculature of the renal and mesenteric beds. Thus, Intropin can increase blood pressure through an inotropic cardiac response or at doses above 20 mcg/kg/min through an additional peripheral vasculature response.

References:
1. Rosenblum, R., Am. Heart J., 87:527-530, 1974.
2. Goldberg, L.I., N.E.J. of Med., 291:707-710, 1974.
3. Harrison, D.C., Am. J. of Card., 35:656-659, 1975.

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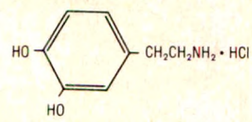
DESCRIPTION: INTROPIN (dopamine HCl) is 3, 4-dihydroxyphenethylamine hydrochloride, a naturally-occurring biochemical catecholamine precursor of norepinephrine. The chemical structure is:



$C_8H_{11}NO_2 \cdot HCl$ Mol. Wt. 189.65

Dopamine hydrochloride is a white, odorless crystalline powder, freely soluble in water and soluble in alcohol. It is sensitive to light, alkalis, iron salts and oxidizing agents.

Each milliliter of sterile, pyrogen-free INTROPIN Injection contains 40 mg. of dopamine hydrochloride (equivalent to 32.96 mg. of dopamine base) in Water for Injection, USP, containing 1% sodium bisulfite as a preservative.

ACTIONS: INTROPIN exerts an inotropic effect on the myocardium resulting in an increased cardiac output. INTROPIN produces less increase in myocardial oxygen consumption than isoproterenol and its use is usually not associated with a tachyarrhythmia. Clinical studies indicate that INTROPIN usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure. Total peripheral resistance at low and intermediate therapeutic doses is usually unchanged. Blood flow to peripheral vascular beds may decrease while mesenteric flow increases. INTROPIN has also been reported to dilate the renal vasculature presumptively by activation of a "dopaminergic" receptor. This action is accompanied by increases in glomerular filtration rate, renal blood flow, and sodium excretion. An increase in urinary output produced by dopamine is usually not associated with a decrease in osmolality of the urine.

INDICATIONS: INTROPIN is indicated for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Where appropriate, restoration of blood volume with a suitable plasma expander or whole blood should be instituted or completed prior to administration of INTROPIN.

Patients most likely to respond adequately to INTROPIN are those in whom physiological parameters, such as urine flow, myocardial function, and blood pressure, have not undergone profound deterioration. Multiclinic trials indicate that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and INTROPIN, the better the prognosis.

Poor Perfusion of Vital Organs – Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. Nevertheless, the physician should also observe the patient for signs of reversal of confusion or comatose condition. Loss of pallor, increase in toe temperature, and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Clinical studies have shown that when INTROPIN is administered before urine flow has diminished to levels approximately 0.3 ml./minute, prognosis is more favorable. Nevertheless, in a number of oliguric or anuric patients, administration of INTROPIN has resulted in an increase in urine flow which in some cases reached normal levels. INTROPIN may also increase urine flow in patients whose output is within normal limits and thus may be of value in reducing the degree of pre-existing fluid accumulation. It should be noted that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Concurrent administration of INTROPIN and diuretic agents may produce an additive or potentiating effect.

Low Cardiac Output – Increased cardiac output is related to INTROPIN's direct inotropic effect on the myocardium. Increased cardiac output at low or moderate doses appears to be related to a favorable prognosis. Increase in cardiac output has been associated with either static or decreased systemic vascular resistance (SVR). Static or decreased SVR associated with low or moderate increments in cardiac output is believed to be a reflection of differential effects on specific vascular beds with increased resistance in peripheral beds (e.g. femoral) and concomitant decreases in mesenteric and renal vascular beds. Redistribution of blood flow parallels these changes so that an increase in cardiac output is accompanied by an increase in mesenteric and renal blood flow. In many instances the renal fraction of the total cardiac output has been found to increase. Increase in cardiac output produced by INTROPIN is not associated with substantial decreases in systemic vascular resistance as may occur with isoproterenol.

Hypotension – Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of INTROPIN, which have little effect on SVR. At high therapeutic doses, INTROPIN's alpha adrenergic activity becomes more prominent and thus may correct hypotension due to diminished SVR. As in the case of other circulatory decompensation states, prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, it is suggested that the physician administer INTROPIN as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

CONTRAINDICATIONS: INTROPIN should not be used in patients with pheochromocytoma.

WARNINGS: INTROPIN should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

Do **NOT** add INTROPIN to any alkaline diluent solution, since the drug is inactivated in alkaline solution.

Patients who have been treated with monamine oxidase (MAO) inhibitors prior to the administration of INTROPIN will require substantially reduced dosage. Dopamine is metabolized by MAO, and inhibition of this enzyme prolongs and potentiates the effect of INTROPIN. The starting dose in such patients should be reduced to at least one-tenth (1/10) of the usual dose.

Usage in Pregnancy – Animal studies have revealed no evidence of teratogenic effects from INTROPIN. In one study, administration of INTROPIN to pregnant rats resulted in a decreased survival rate of the newborn and a potential for cataract formation in the survivors. The drug may be used in pregnant women when, in the judgment of the physician, the expected benefits outweigh the potential risk to the fetus.

Usage in Children – The safety and efficacy of this drug in children has not been established. INTROPIN has been used in a limited number of pediatric patients, but such use has been inadequate to fully define proper dosage and limitations for use. Further studies are in progress.

PRECAUTIONS: Avoid Hypovolemia – Prior to treatment with INTROPIN, hypovolemia should be fully corrected, if possible, with either whole blood or plasma as indicated.

Decreased Pulse Pressure – If a disproportionate rise in the diastolic pressure (i.e. a marked decrease in the pulse pressure) is observed in patients receiving INTROPIN, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

Extravasation – INTROPIN should be infused into a large vein whenever possible to prevent the possibility of extravasation into tissue adjacent to the infusion site. Extravasation may cause necrosis and sloughing of surrounding tissue. Large veins of the antecubital fossa are preferred to veins in the dorsum of the hand or ankle. Less suitable infusion sites should be used only if the patient's condition requires immediate attention. The physician should switch to more suitable sites as rapidly as possible. The infusion site should be continuously monitored for free flow.

Occlusive Vascular Disease – Patients with a history of occlusive vascular disease (for example, atherosclerosis, arterial embolism, Raynaud's disease, cold injury, diabetic endarteritis, and Buerger's disease) should be closely monitored for any changes in color or temperature of the skin in the extremities. If a change in skin color or temperature occurs and is thought to be the result of compromised circulation to the extremities, the benefits of continued INTROPIN infusion should be weighed against the risk of possible necrosis. This condition may be reversed by either decreasing or discontinuing the rate of infusion.

IMPORTANT – Antidote for Peripheral Ischemia: To prevent sloughing and necrosis in ischemic areas, the area should be infiltrated as soon as possible with 10 to 15 ml. of Saline solution containing from 5 to 10 mg. of Regitine® (brand of phentolamine), an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, and the solution liberally infiltrated throughout the ischemic area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, phentolamine should be given as soon as possible after the extravasation is noted.

Avoid Cyclopropane or Halogenated Hydrocarbon Anesthetics – Cyclopropane or halogenated hydrocarbon anesthetics increase cardiac autonomic irritability and therefore may sensitize the myocardium to the action of certain intravenously administered catecholamines. This interaction appears to be related both to pressor activity and to beta adrenergic stimulating properties of these catecholamines. Therefore, as with certain other catecholamines, and because of the theoretical arrhythmogenic potential, INTROPIN should be used with EXTREME CAUTION in patients inhaling cyclopropane or halogenated hydrocarbon anesthetics.

Careful Monitoring Required – Close monitoring of the following indices – urine flow, cardiac output and blood pressure – during INTROPIN infusion is necessary as in the case of any adrenergic agent.

ADVERSE REACTIONS: The most frequent adverse reactions observed in clinical evaluation of INTROPIN included ectopic beats, nausea, vomiting, tachycardia, anginal pain, palpitation, dyspnea, headache, hypotension, and vasoconstriction. Other adverse reactions which have been reported infrequently were aberrant conduction, bradycardia, piloerection, widened QRS complex, azotemia, and elevated blood pressure.

DOSAGE AND ADMINISTRATION:

WARNING: This is a potent drug: It must be diluted before administration to patient.

Suggested Dilution – Transfer contents of one ampul (5 ml. containing 200 mg. INTROPIN) by aseptic technique to either a 250 ml. or 500 ml. bottle of one of the following sterile intravenous solutions:

1) Sodium Chloride Injection, USP
2) Dextrose 5% Injection, USP
3) Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
4) 5% Dextrose in 0.45% Sodium Chloride Solution
5) Dextrose (5%) in Lactated Ringer's Solution
6) Sodium Lactate (1/6 Molar) Injection, USP
7) Lactated Ringer's Injection, USP

These dilutions will yield a final concentration for administration as follows:
250 ml. dilution contains 800 mcg./ml. of INTROPIN
500 ml. dilution contains 400 mcg./ml. of INTROPIN

INTROPIN has been found to be stable for a minimum of 24 hours after dilution in the sterile intravenous solutions listed above. However, as with all intravenous admixtures, dilution should be made just prior to administration.

Do **NOT** add INTROPIN Injection to 5% Sodium Bicarbonate or other alkaline intravenous solutions, since the drug is inactivated in alkaline solution.

Rate of Administration – INTROPIN, after dilution, is administered intravenously through a suitable intravenous catheter or needle. An i.v. drip chamber or other suitable metering device is essential for controlling the rate of flow in drops/minute. Each patient must be individually titrated to the desired hemodynamic and/or renal response with INTROPIN. In titrating to the desired increase in systolic blood pressure, the optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the hemodynamic condition is stabilized.

Administration at rates greater than 50 mcg./kg./min. have safely been used in advanced circulatory decompensation states. If unnecessary fluid expansion is of concern, adjustment of drug concentration may be preferred over increasing the flow rate of a less concentrated dilution.

Suggested Regimen:

1. When appropriate, increase blood volume with whole blood or plasma until central venous pressure is 10 to 15 cm H_2O or pulmonary wedge pressure is 14-18 mm Hg.

2. Begin administration of diluted solution at doses of 2-5 mcg./kg./minute INTROPIN in patients who are likely to respond to modest increments of heart force and renal perfusion.

In more seriously ill patients, begin administration of diluted solution at doses of 5 mcg./kg./minute INTROPIN and increase gradually using 5 to 10 mcg./kg./minute increments up to 20 to 50 mcg./kg./minute as needed. If doses of INTROPIN in excess of 50 mcg./kg./minute are required, it is suggested that urine output be checked frequently. Should urine flow begin to decrease in the absence of hypotension, reduction of INTROPIN dosage should be considered. Multiclinic trials have shown that more than 50% of the patients were satisfactorily maintained on doses of INTROPIN less than 20 mcg./kg./minute. In patients who do not respond to these doses with adequate arterial pressures or urine flow, additional increments of INTROPIN may be employed in an effort to produce an appropriate arterial pressure and central perfusion.

3. Treatment of all patients requires constant evaluation of therapy in terms of the blood volume, augmentation of myocardial contractility, and distribution of peripheral perfusion. Dosage of INTROPIN should be adjusted according to the patient's response, with particular attention to diminution of established urine flow rate, increasing tachycardia or development of new dysrhythmias as indices for decreasing or temporarily suspending the dosage.

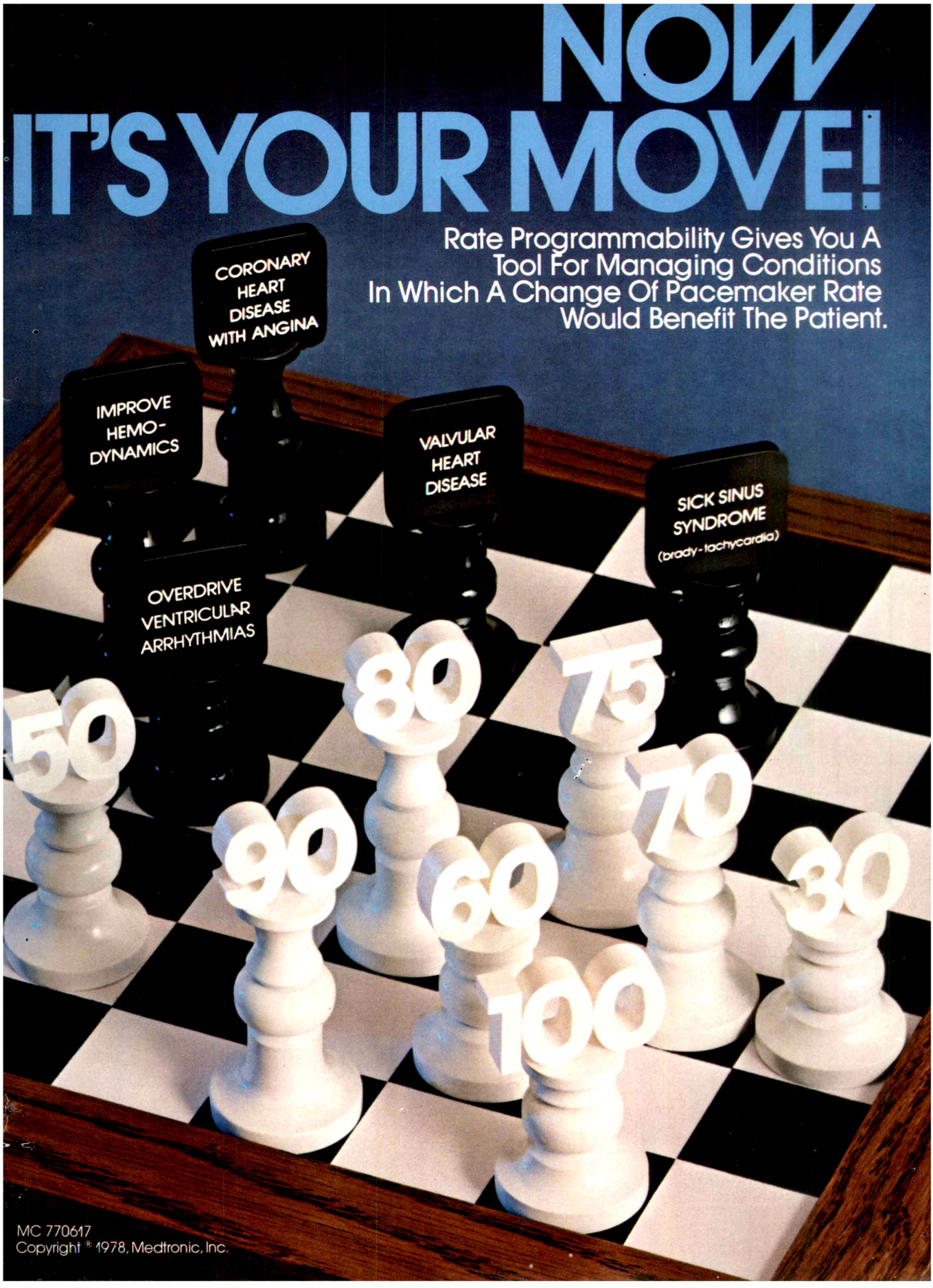
4. As with all potent intravenously administered drugs, care should be taken to control the rate of administration so as to avoid inadvertent administration of a bolus of drug.

OVERDOSAGE: In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce rate of administration or temporarily discontinue INTROPIN until patient's condition stabilizes. Since INTROPIN's duration of action is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha adrenergic blocking agent, phentolamine, should be considered.

HOW SUPPLIED: 5 ml. ampuls containing 40 mg. dopamine HCl per milliliter.

September, 1975

ARNAR-STONE LABORATORIES, INC.
Mount Prospect, Illinois 60056
A Subsidiary of American Hospital Supply Corporation


NOW
IT'S YOUR MOVE!
Rate Programmability Gives You A Tool For Managing Conditions In Which A Change Of Pacemaker Rate Would Benefit The Patient.
CORONARY HEART DISEASE WITH ANGINA
IMPROVE HEMO-DYNAMICS
VALVULAR HEART DISEASE
SICK SINUS SYNDROME (brady-tachycardia)
OVERDRIVE VENTRICULAR ARRHYTHMIAS
50
80
75
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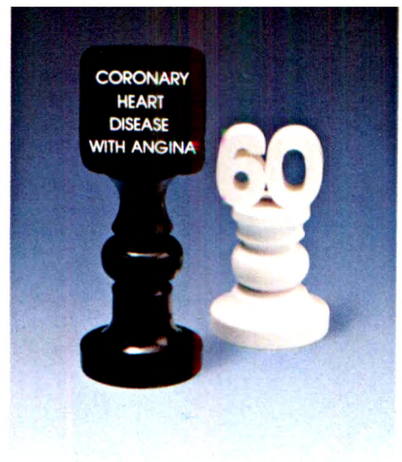
THERE ARE AT LEAST FIVE APPLICATIONS IN WHICH HAVING THE FLEXIBILITY OF CHANGING PACED RATE CAN PROVIDE MORE VERSATILITY IN PATIENT MANAGEMENT.

These applications are:

1. Sick Sinus Syndrome (brady-tachycardia).
2. Coronary heart disease with angina pectoris.
3. Valvular heart disease.
4. To overdrive ventricular arrhythmias.
5. To improve hemodynamics.

In each of these, having the ability to change the pacing rate can preserve, maintain or improve the quality of life for pacemaker patients. Furthermore, because of the potential longevity of lithium pacemakers, the physician can take advantage of the greater flexibility provided by rate programmability to respond to the patient's changing medical condition during the pulse generator service life.



USING RATE PROGRAMMABLE PACEMAKERS IN CORONARY HEART DISEASE WITH ANGINA PECTORIS

Not infrequently, the patient in whom pacing is indicated presents with coronary artery disease and angina pectoris.

Angina may be occurring as a consequence of heart rate exceeding the ability of the coronary artery network to provide adequate circulation to myocardial tissue. Since heart tissues receive nutrients during diastole, it is felt that a slower heart rate and a corresponding longer diastolic period may provide enhanced opportunity for energy and oxygen transfer to myocardial tissue.

In any event, a rate programmable pacemaker permits evaluation for clinical symptoms at various rates and can permit selection of a pacing rate which is not likely to provoke angina, while providing the patient with adequate exertional status.

THE APPLICATION OF RATE PROGRAMMING IN BRADY-TACHYCARDIA (SICK SINUS SYNDROME).

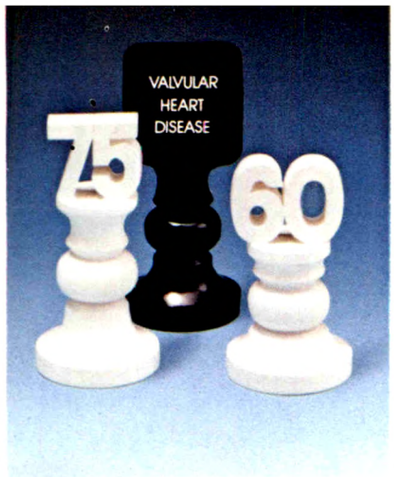
After the physician has determined that artificial heart pacemaking is the treatment of choice for the patient with brady-tachycardia, he may contemplate application of a rate-programmable pacemaker to treat this disease.

Because brady-tachycardia may be a progressive disease, it is often appropriate to implant a rate-programmable pacemaker.

For example, in the early stages of the disorder, the patient may require pacing for just a few seconds a month when the intrinsic rate drops below a rate which the physician has determined provides adequate cardiac output. In such a situation, the pacemaker is set at a low rate (i.e., 50 or 60 ppm) to provide an underlying safe rhythm, but which allows the patient the benefit of his normal atrial ventricular contraction sequence.

Sick sinus syndrome at times is a progressive disorder which may result in a slowing of the patient's normal sinus rhythm. This slowing may be gradual or sudden. Frequently, it is accompanied by a tendency towards a more unreliable rhythm. The patient, thus, increases his or her reliance on the pacemaker for adequate heart rate.

Rate programming at increasingly higher rates may help maintain cardiac output at adequate levels when the pacemaker is needed to provide the dominant rhythm. An increase in pacemaker rate may also be needed to prevent the emergence of a less suitable tachyarrhythmia.



THE APPLICATION OF RATE PROGRAMMABLE PULSE GENERATORS IN VALVULAR HEART DISEASE

The clinical course for pacemaker patients with valvular heart disease is complex and unpredictable.

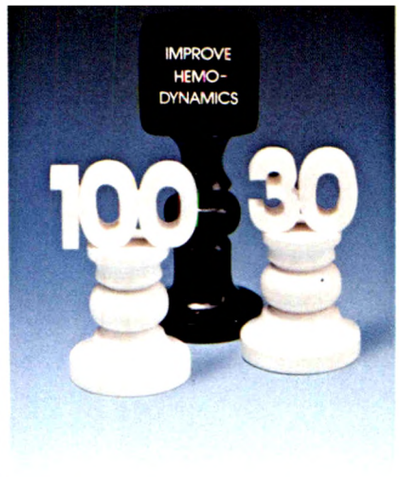
Many of these patients require a pacemaker prior to operation for their valve lesion.

The patient with aortic stenosis may need to have his rate adjusted to a slow level to allow for complete emptying of the ventricle. Too fast a rate increases ventricular pressure and restricts the flow of blood from the coronary arteries to the endocardium, resulting in subendocardial ischemia. There is some evidence that pacing at typical fixed pacemaker rates may actually cause patients with aortic stenosis to lose cardiac output and have decreased perfusion pressure.

On the other hand, the patient with aortic insufficiency has regurgitation backwards into the ventricle. A slow rate allows more blood to flow backwards, increasing volume and ventricular pressure. This also restricts blood flow from the coronary arteries to the endocardium, again resulting in subendocardial ischemia. A faster paced rate may help control the condition. Of course, the best rate for perfusing the endocardium for either condition varies considerably between patients.

Rate requirements will probably change a great deal when a prosthetic valve replacement is made.

Typically, any patient with valvular heart disease who requires a pacemaker could benefit from the flexibility a rate-programmable pacemaker offers in this complex, unpredictable disorder.



CHANGING RATE TO ENHANCE THE METABOLIC STATE THROUGH IMPROVED HEMODYNAMICS

Conditions of disease, or certain medical treatments, can affect a patient's metabolic requirements. Pacemaker patients are, because of their age and underlying heart disease, prone to various medical problems, including myocardial infarction, angina and congestive heart failure.

By having the ability to alter the diseased or ill patient's heart rate, the physician can optimize the rate for maximum cardiac output and organ perfusion without affecting (or with minor effects) on myocardial oxygen uptake. Also, in some MI patients a rate can be found which produces increased cardiac output with decreased left ventricular filling pressure. Rate changes may also affect and improve a patient's mental state and enhance the ability to perform even mild exercise. When a pacemaker is implanted, the patient is ill (i.e. bed-ridden). An adequate rate under those conditions may not be adequate when the patient is up and about.

USE OF RATE PROGRAMMABLE PACEMAKERS TO CONTROL VENTRICULAR ARRHYTHMIAS

Ectopic ventricular activity can be suppressed by permanent pacing. However, the slowest paced rate at which ventricular arrhythmias will be controlled is unpredictable, and changeable. It is not unusual for the rate at which PVC's occur to change as the patient's underlying heart disease progresses.

Pacing in the presence of PVC's often involves considerable adjusting of rate as the physician determines the paced rate which will be just slightly higher than the rate at which the ectopic foci discharge. This rate may involve a compromise, for an optimal rate for achieving maximal cardiac output may not coincide with the best rate for suppressing ectopic activity. Indeed some pacemaker rates tend to excite reentry pathways causing the extra-systole.

For these reasons, having the opportunity to change rate can assist the physician in arrhythmia control.

Medtronic

Helping You
Help The Pacemaker Patient

MEDTRONIC'S XYREL®-VP PACING SYSTEM

Offering you simplicity, ease of operation, and seven pacing rates plus one diagnostic rate for patient safety.

The Xyrel®-VP. It's as easy to program as 1, 2, 3.

1. Set the desired pacing rate.
2. Position the programmer over the pacemaker.
3. Press and release the program activate button.*

Constant Energy—A programmed pulse width increase as battery voltage declines provides for constant pacemaker energy output throughout its effective service life.

Constant Rate—Xyrel®-VP pacemaker rate stays at the rate at which you programmed it. It won't decrease as battery voltage slowly drops. However, once voltage declines to the point at which the pacemaker should be replaced, an easily detected rate decrease occurs over one to six months (typically). There are many other performance and safety features that are part of every Xyrel®-VP pulse generator.

*To avoid inadvertent programming to the 30 ppm rate, an additional step is necessary when this rate is desired.

Send in the coupon for details. Or see your local Medtronic representative.

MEDTRONIC IMPLANTABLE PULSE GENERATORS

INTENDED USES Ventricular pacing using an implantable ventricular pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation or conduction disorders leading to bradyarrhythmias, tachyarrhythmias and heart block (see product labeling for detailed list of intended uses).

CONTRAINDICATIONS There are no known contraindications to the use of pacing as a therapeutic modality for the control of heart rate. The patient's age and medical condition, however, may dictate the particular pacing systems and implantation procedure used by the physician.

WARNINGS Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of unipolar pulse generators or bipolar pulse generctors implanted in the unipolar mode because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator.

PRECAUTIONS The physician should be aware that all pulse generators will ultimately cease to function, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, and elevated thresholds, and that proper operation may be affected by electrical interference from equipment using electrical energy, or medical complications.

SIDE EFFECTS Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.

MEDTRONIC HAS COMPILED MORE COMPLETE INFORMATION ON THE APPLICATIONS OF RATE PROGRAMMABILITY TO PACEMAKER PATIENTS

If you would like a copy of Medtronic's information guide on the applications of rate programmability where permanent ventricular pacing is indicated, please send in the coupon below.

Mail To: **Medtronic, Inc., 3055 Old Highway Eight, P.O. Box 1453 Minneapolis, MN 55440 USA**

☐ I would like more information on the applications of rate programmability.

☐ I would like more information on the Medtronic Xyrel®-VP programmable pacing system.

☐ Please have a representative call.

Name_____ Specialty_____

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Medtronic

Helping You
Help The Pacemaker Patient

MSD ANNOUNCES

NEW

TABLETS

Aldoril® D30

D, the Roman numeral for 500, stands for 500 mg ALDOMET® (Methyldopa, MSD) and 30 for 30 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

NEW

TABLETS

Aldoril® D50

D, the Roman numeral for 500, stands for 500 mg ALDOMET® (Methyldopa, MSD) and 50 for 50 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

MSD
MERCK SHARP & DOHME

For a brief summary of prescribing information, please see last page of this advertisement.

Practical antihypertensive therapy.

for a broad range of active patients*

ALDORIL®, containing ALDOMET® (Methyldopa, MSD) and HydroDIURIL® (Hydrochlorothiazide, MSD)—two highly effective complementary agents—offers:

b.i.d. convenience for many patients

b.i.d. doses can be used for many patients.

more economical therapy

ALDORIL may offer more economical therapy than individual prescriptions for both HydroDIURIL and ALDOMET.

daily activities usually not affected

Exercise hypotension and diurnal blood pressure variations rarely occur. There is less frequent symptomatic postural hypotension than with many other antihypertensive agents.

no overshoot

Since both components of ALDORIL have a relatively short duration of action, withdrawal is followed by a return of hypertension usually within 48 hours. This is not complicated by an overshoot of blood pressure.

favorable cardiac profile

Neither component of ALDORIL usually has any direct effect on cardiac function in long-term therapy—cardiac output is usually maintained.

ALDORIL is contraindicated in active hepatic disease; anuria; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs; if previous methyldopa therapy has been associated with liver disorders.

In patients with renal disease, thiazides may precipitate azotemia. Use with caution in patients with severe renal disease or impaired hepatic function.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, see the brief summary of prescribing information.

NEW

TABLETS

Aldoril® D30

containing 500 mg ALDOMET® (Methyldopa, MSD) and 30 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

NEW

TABLETS

Aldoril® D50

containing 500 mg ALDOMET® (Methyldopa, MSD) and 50 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

ALSO AVAILABLE

TABLETS

ALDORIL®-25 containing 250 mg ALDOMET® (Methyldopa, MSD) and 25 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

TABLETS

ALDORIL®-15 containing 250 mg ALDOMET® (Methyldopa, MSD) and 15 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

*As a fixed combination, ALDORIL is not indicated for initial therapy since hypertension requires therapy titrated to the individual patient's needs. If an available strength of ALDORIL meets the patient's titrated needs, the combination drug may be more convenient in patient management. Therapy should be reevaluated as necessary.

MSD
MERCK SHARP & DOHME

For a brief summary of prescribing information, please see following page.

Antihypertensive TABLETS

New ALDORIL® D50
methyldopa 500 mg and hydrochlorothiazide 50 mg

Antihypertensive TABLETS

New ALDORIL® D30
methyldopa 500 mg and hydrochlorothiazide 30 mg

Antihypertensive TABLETS

ALDORIL®-25
methyldopa 250 mg and hydrochlorothiazide 25 mg

Antihypertensive TABLETS

ALDORIL®-15
methyldopa 250 mg and hydrochlorothiazide 15 mg

WARNING

This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be re-evaluated as conditions in each patient warrant.

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see **Warnings**); anuria; routine use in an otherwise healthy pregnant woman with or without mild edema; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs.

Warnings: METHYLDOPA—**It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.**

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within the first three weeks of therapy, sometimes with eosinophilia or abnormalities in one or more liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually within the first two to three months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, reversible reduction of white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Follow patients carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

HYDROCHLOROTHIAZIDE—Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity; read circulars for lithium preparations before use of such concomitant therapy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks.

Methyldopa and thiazides cross the placental barrier and appear in cord blood.

No unusual adverse reactions have been reported in association with the use of methyldopa during pregnancy. Although no obvious teratogenic effects have been reported, the possibility of fetal injury cannot be excluded.

The hazards of thiazides crossing the placental barrier include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in adults. Methyldopa and thiazides appear in breast milk. Patients taking ALDORIL should not nurse.

Precautions: METHYLDOPA—Should be used with caution in patients with history of previous liver disease or dysfunction (see **Warnings**). May interfere with measurement of urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites. Involuntary choreoathetotic movements have been observed in patients with severe bilateral cerebrovascular disease. If such movements occur, stop the drug. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

HYDROCHLOROTHIAZIDE—Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance: namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroids or ACTH, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

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HYDROCHLOROTHIAZIDE—*Gastrointestinal system:* Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis. *Central nervous system:* Dizziness, vertigo, paresthesias, headache, xanthopsia. *Hematologic:* Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. *Cardiovascular:* Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics). *Hypersensitivity:* Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions. *Other:* Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: Tolerance may occur, usually between the second and third month of therapy. Increasing dosage of either component separately or together frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

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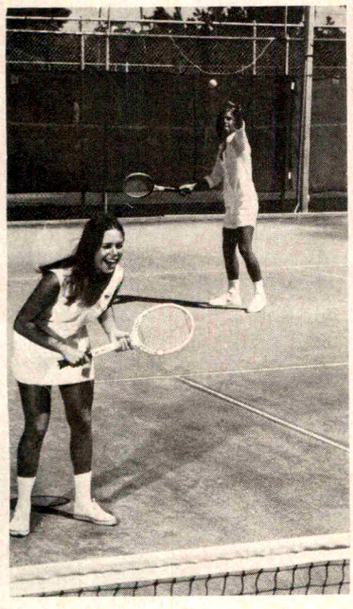
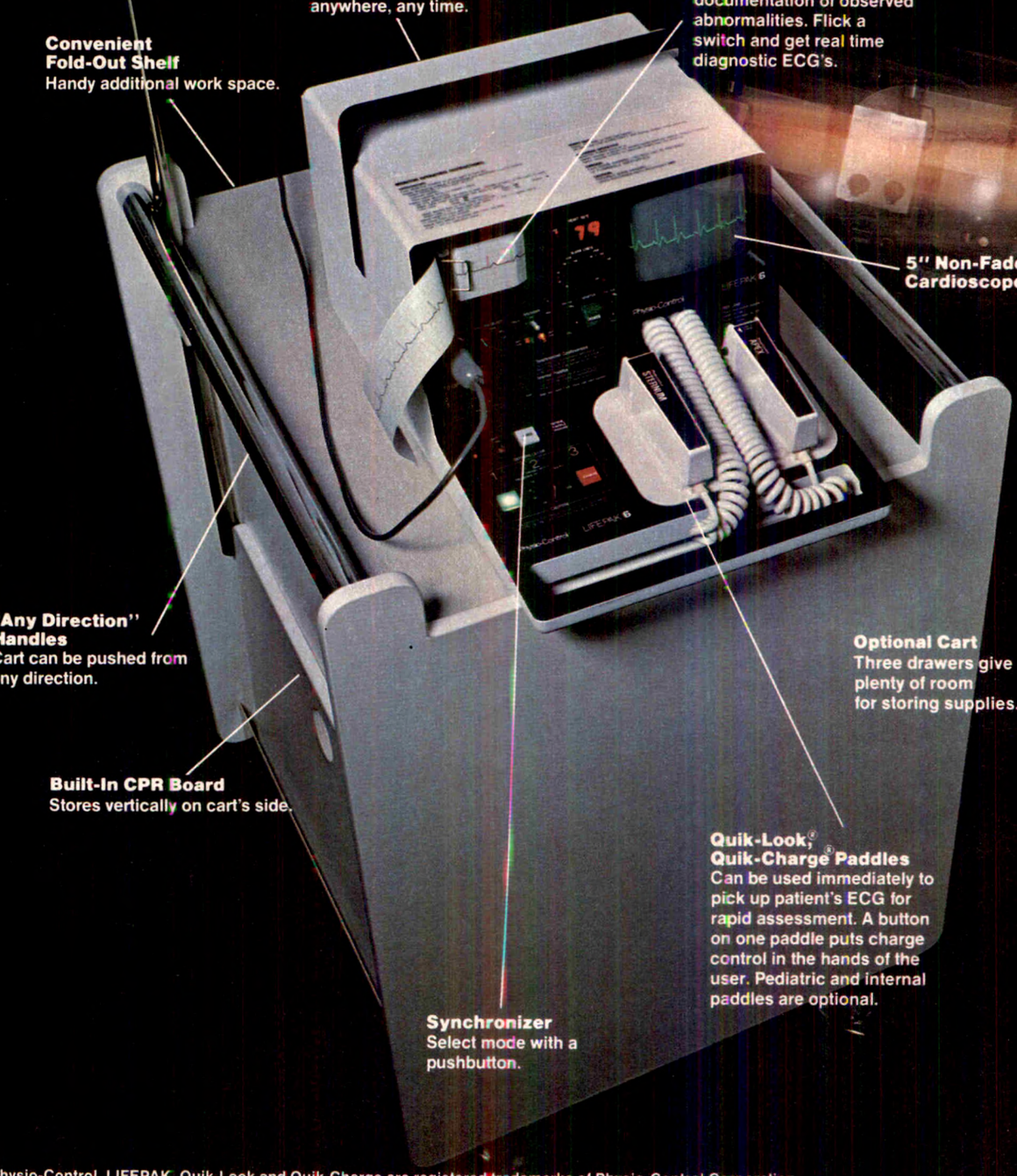


ADAPTABLE



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Submaximal Exercise Testing After Acute Myocardial Infarction: Myocardial Scintigraphic and Electrocardiographic Observations

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The relation between global and regional left ventricular function and electrocardiographic signs of ischemia at rest and during submaximal supine exercise was studied in 27 patients 2 to 3 weeks after acute myocardial infarction. Dynamic myocardial scintigraphy was performed at rest and during submaximal exercise utilizing an in vivo method of labeling red blood cells with technetium-99m pertechnetate. Gated radionuclide blood pool scintigrams were obtained in a modified left anterior oblique, and in some patients also in the right anterior oblique projection, to measure left ventricular ejection fraction and segmental wall motion. Electrocardiographic monitoring of heart rate and rhythm was provided during the exercise. The submaximal exercise test was terminated when the patient's heart rate reached 125 beats/min or if angina, malignant ventricular ectopy or electrocardiographic evidence of myocardial ischemia developed before this rate was reached.

The data demonstrate that patients with a recent anterior myocardial infarct, in contrast to patients with a recent inferior or nontransmural infarct, manifest a significant reduction in left ventricular ejection fraction with submaximal exercise. Of the eight patients with an anterior infarct, seven had segmental wall motion abnormalities at rest. Four of these eight manifested more severe abnormalities with submaximal exercise; three had abnormalities at rest that did not change with exercise. Four of the eight had a positive electrocardiographic response during exercise (two were taking digoxin). Of these four, only two had more marked wall motion abnormalities with effort. Of the 13 patients with an inferior infarct, 11 had apparently normal wall motion in the modified left anterior oblique projection at rest, including 2 who manifested segmental wall motion abnormalities with submaximal exercise; the 2 remaining patients had wall motion abnormalities at rest that, on exercise, became more marked in one and were unchanged in one. Four of the 13 had a positive electrocardiographic response with exercise (one was taking digoxin); only one of these had a detectably more severe wall motion abnormality with exercise. Of the six patients with a nontransmural infarct, four had no identifiable wall motion abnormalities at rest; in one of these, an abnormality developed with exercise. The remaining two patients had wall motion abnormalities at rest; in one, a positive electrocardiographic ischemic response developed with exercise.

Patients with an anterior infarct appear to have a different functional ventricular response to submaximal exercise at the time of hospital discharge than patients with an inferior or nontransmural infarct. To identify ischemic responses with submaximal exercise in these patients one should ideally use both electrocardiographic monitoring and dynamic myocardial scintigraphy.

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Traditionally, the electrocardiogram has been utilized to monitor patients performing treadmill or bicycle exercise to assess the presence of physiologically important coronary artery disease.[1,2] This approach has certain limitations, including the potential development of false positive or false negative responses[3,4] and the uncertain significance of ST-T wave changes in patients with an intraventricular conduction defect or ventricular hypertrophy and in those taking digitalis or other cardiac medications.[1,2] Recently Green, Borer and their co-workers[5,6] described exercise testing in patients utilizing myocardial scintigraphy to document segmental wall motion abnormalities that might develop as a consequence of regional ischemia and also to measure ventricular ejection fraction during exercise stress. In this study we evaluated the relation between global and regional left ventricular function and electrocardiographic signs of ischemia at rest and during supine submaximal exercise in patients immediately before hospital discharge after myocardial infarction. Our intent was to establish the advantages and disadvantages of both myocardial scintigraphy and electrocardiographic monitoring in assessing the development of signs of ischemia in such patients.

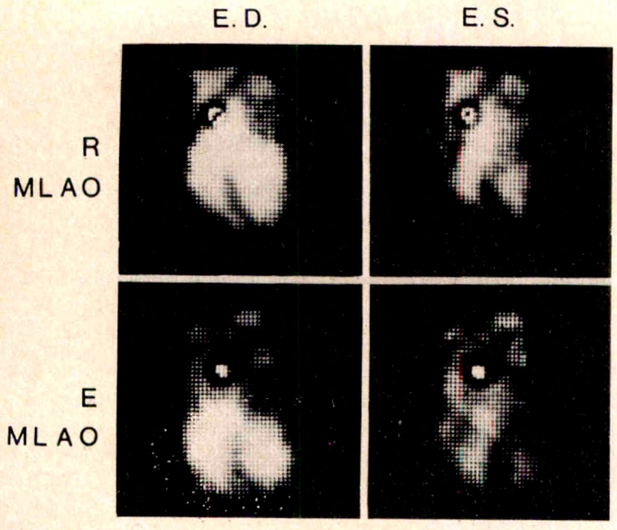


FIGURE 1. Normal blood pool scintigrams at end-diastole (E.D.) and end-systole (E.S.) obtained at rest (R) and during exercise (E) in a modified left anterior oblique projection with 15° caudal angulation (MLAO). Note the marker used to determine the extent of patient motion during exercise.

Materials and Methods

Patients: Twenty-seven patients, 19 men and 8 women with a mean age of 59 years (range 49 to 89), were studied after they gave informed consent. Eight patients had an acute anterior transmural myocardial infarct, 13 an acute inferior transmural myocardial infarct and 6 an acute subendocardial myocardial infarct. The diagnosis of myocardial infarction was based on electrocardiographic, enzymatic (creatine kinase [CK] and CK-B isoenzyme)[7] and technetium-99m stannous pyrophosphate myocardial scintigraphic data[8] documenting the presence of recent myocardial infarction. The patients exercised submaximally on days 13 to 37 (mean 17 days) after their myocardial infarct and immediately before discharge from the hospital. It has been our practice to obtain submaximal exercise tests in patients with myocardial infarction immediately before hospital discharge in order to be certain that modest effort does not produce life-threatening ventricular ectopy or electrocardiographic evidence of severe myocardial ischemia.[9] Nine of these patients, who had no subsequent signs or symptoms of new myocardial damage, returned electively

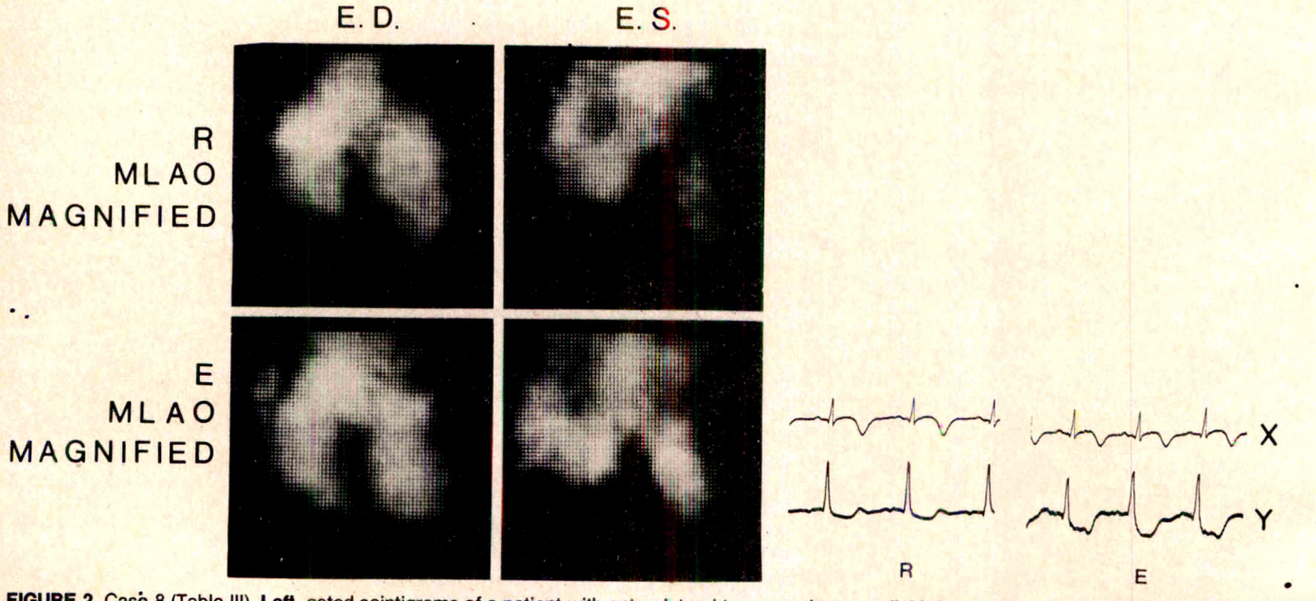


FIGURE 2. Case 8 (Table III). **Left,** gated scintigrams of a patient with anterolateral transmural myocardial infarction showing apical akinesia at rest and somewhat more prominent apical dyskinesia with submaximal exercise. **Right,** positive electrocardiographic response in orthogonal lead Y obtained during submaximal exercise. Abbreviations as in Figure 1.

for repeat exercise testing 6 weeks after the initial examination. These nine patients had undergone gradual rehabilitation and resumption of normal activity at an individually determined rate after their return home.

Exercise testing: The patients underwent submaximal exercise testing in the supine position with continuous electrocardiographic monitoring of heart rhythm and rate and periodic measurements of blood pressure. The exercise test was terminated after a heart rate of 125 beats/min was attained or if angina, malignant ventricular ectopy or electrocardiographic evidence of myocardial ischemia developed before this rate was reached. The test protocol consisted of bicycle (Elema Schonander Type AM 368) exercise over an increasing range of work load values (50, 150, 300, 350 and 400 kilopond-meters/min); approximately 5 to 7 minutes was spent at each work load. In patients able to exercise at the highest work load for only 1 to 2 minutes before the development of angina, marked fatigue, malignant ventricular ectopy or electrocardiographic manifestations of ischemia, the previous work load and myocardial scintigraphic images and electrocardiographic responses were utilized for experimental comparisons.

Myocardial scintigraphic imaging: Radionuclide blood pool scintigrams were obtained with a modification of an in vivo red blood cell labeling technique we[10] recently described. In brief, 5 mg of stannous pyrophosphate was injected intravenously. Approximately 25 to 30 minutes later, 15 mCi of technetium-99m pertechnetate was injected intravenously. Twenty minutes later myocardial imaging was begun to obtain electrocardiographic gated radionuclide blood pool scintigrams in a left anterior oblique projection with 15° caudal angulation at rest (a few patients also had images obtained at rest in the right anterior oblique projection) and then during supine bicycle exercise. Electrocardiographic gated images were acquired at end-diastole (0.05 second before the R wave) and end-systole (0.05 second after subsidence of the T wave). A marker was placed on each patient's chest wall to serve as a reference point so that any excessive movement of the chest wall during exercise could be identified. Radionuclide blood pool scintigrams were obtained with a portable General Electric gamma camera and processed on a General Electric Med II computer (Fig. 1). A minimum of 300,000 counts was collected for each systolic and diastolic frame obtained at rest. During exercise, for the majority of patients, it was possible to collect only approximately 200,000 counts per frame. However, in every instance only those scintigraphic images that had clearly defined left ventricular boundaries in both the resting and exercise studies were utilized for ventricular wall motion and ejection fraction measurements (Fig. 1 to 3).

Ventricular wall motion and outline analysis: Images were acquired as 64 by 64 digital matrixes. Before ventricular outlines were identified for wall motion analysis, the images were contrast-enhanced by subtraction of a constant level of background activity, digitally filtered to smooth noise variations, and then expanded. For wall motion analysis, the images were expanded linearly by a factor of 2 (a 32 by 32 element array including the left ventricle was chosen and expanded to a full 64 by 64 element interpolated array). The images were not expanded for volume and ejection fraction determinations.

Ventricular outlines were designated manually by one observer (J.P.). A similar manual outlining method was used in area-length volume determinations by Strauss and colleagues,[11] although their images were not in the form of digitized matrixes. Ventricular outlines determined from a discrete array are inevitably somewhat inaccurate as estimates of continuous outlines. On the other hand, the computer processing made possible by image digitization can help identify the ventricular boundary when its position is somewhat uncertain.

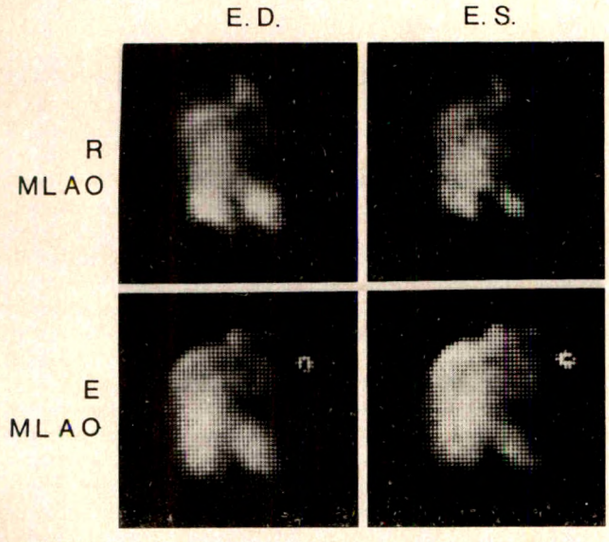


FIGURE 3. Case 9 (Table III). Gated scintigrams of a patient with posteroinferior myocardial infarction indicating normal left ventricular wall motion at rest (R) and apical akinesia with submaximal exercise (E). Abbreviations as in Figure 1.

TABLE I

Preliminary Study: Comparison of Left Ventricular Ejection Fraction and Segmental Wall Motion Data Obtained With Scintigraphic and Angiographic Techniques in 17 Patients

Case no.	Left Ventricular Ejection Fraction (%)		Left Ventricular Wall Motion	
	Angiographic	Scintigraphic	Angiographic	Scintigraphic
1	51	51	Normal	Normal
2	47	39	Anterior akinesia	Anteroapical akinesia
3	72	75	Normal	Normal
4	68	73	Normal	Normal
5	55	49	Anteroapical dyskinesia	Anteroapical dyskinesia
6	45	45	Posteroinferior akinesia	Normal
7	43	49	Posteroinferior hypokinesia	Apical akinesia
8	44	56	Anteroapical dyskinesia	Anterior dyskinesia
9	34	32	Apical dyskinesia	Anteroapical dyskinesia
10	59	53	Posteroinferior akinesia	Lateral akinesia
11	84	74	Normal	Normal
12	55	66	Normal	Normal
13	75	69	Normal	Normal
14	78	75	Normal	Normal
15	56	59	Normal	Septal hypokinesia
16	58	68	Anteroapical hypokinesia	Anteroapical dyskinesia
17	48	46	Diffuse hypokinesia	Diffuse hypokinesia

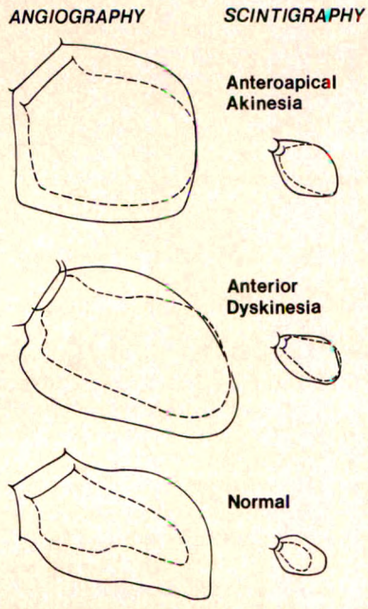


FIGURE 4. Selected examples of the comparison of left ventricular boundaries determined angiographically **(left)** and scintigraphically **(right)** in three patients.

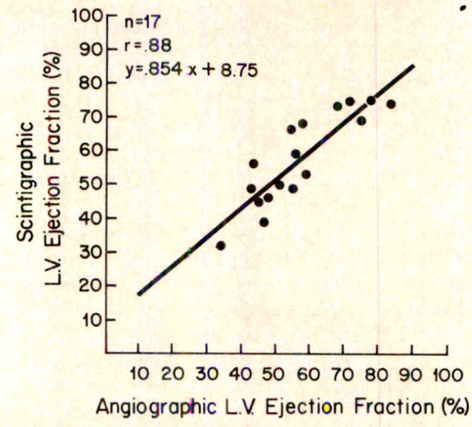


FIGURE 5. Correlation between angiographic and gated blood pool scintigraphic measurements of left ventricular (L.V.) ejection fraction in 17 patients. n = number of patients; r = correlation coefficient.

A portion of the right ventricle sometimes overlies the inferior margin of the left ventricle in the right anterior oblique view. Even when this occurred, the left ventricular inferior boundary was often easily identifiable; when it was not easily identifiable, we believe that the resulting error was small, in view of the close correlation found between the ejection fractions obtained with scintigraphy and contrast angiography.

Reliability of the technique: The reliability of the method is demonstrated by the close correlation of left ventricular ejection fraction measurements obtained with scintigraphy and contrast ventriculography and by its intraobserver repeatibility.

Correlation with contrast angiographic measurements: In 17 additional patients undergoing cardiac catheterization for various reasons, including suspected coronary artery disease, preliminary studies were conducted to verify that our scintigraphic measurements of left ventricular ejection fraction and segmental wall motion correlated with the same information obtained angiographically (Table I) (Fig. 4). These patients were studied before and 1 to 25 days (mean 7.4 days) after cardiac catheterization. None of them demonstrated any important clinical change in the interval between procedures.

Comparison of scintigraphic and angiographic wall motion was performed as follows: After the images were processed and magnified as described previously, the boundaries of the left ventricle were traced manually on the screen during both end-diastole and end-systole. A Polaroid® picture was then taken of the superimposed outlines. Angiographic ventricular outlines were traced from projected 35 mm films. The left ventricular ejection fraction was measured with the single plane area-length method, both scintigraphically and angiographically. We found significant correlation between left ventricular ejection fraction determined scintigraphically and angiographically in these patients (Table I) (Fig. 5).

Repeatability: Estimates of volume measurement error were performed in the following way: Two observers performed five to six separate measurements of end-diastolic and end-systolic volumes in five (Observer 1) and eight (Observer 2) gated blood pool studies. Because at least three measurements are usually averaged in estimating ejection fraction, the agreement between successive groups of three measurements by the same observer was analyzed. In the eight studies analyzed with six separate measurements, there was no statistically significant difference ($P > 0.05$ by t test) between the means of successive groups of three ejection fraction measurements. Mean intraobserver variation was 3 ± 2.8 percent (standard deviation) with a range of 0 to 9 percent.

Electrocardiographic measurements: In the first 19 patients (70 percent), the electrocardiographic recordings were obtained utilizing a system of seven leads during exercise (I, II, III, aVR, aVL, aVF and V_1), all seven leads being recorded at the peak of exercise. Subsequently, five patients (19 percent) were studied with 12 electrocardiographic leads (limb and precordial leads) recorded at the peak level of exercise. The last three patients studied (11 percent) were evaluated utilizing an orthogonal system (X, Y and Z leads) with electrocardiographic recording for later computer analysis. The electrocardiographic response was considered positive if S-T segment displacement was equal to or greater than 1 mm when measured 0.08 second after the J point in downsloping and horizontal segments.

Ejection fraction and segmental wall motion measurements: Scintigraphic left ventricular ejection fraction was measured at rest and at the peak level of exercise in the modified left anterior oblique projection utilizing the area-length method.[12,13] Left ventricular segmental wall motion abnormalities were considered to show an abnormal response consistent with ischemia during exercise when a new abnormality appeared or when an abnormality at rest became more severe during exercise. In studying left ventricular segmental wall motion, the boundaries of the left ventricle as observed during end-systole and end-diastole were traced from the computer display, care being taken to identify the aortic valve plane as precisely as possible. A qualitative analysis of segmental wall motion in the septal, lateral and apical regions in both the resting and exercise studies was obtained. In 18 patients a quantitative analysis of segmental wall motion from the traced end-systolic and end-diastolic images was made as follows: Systolic and diastolic boundaries of the left ventricle

TABLE II

Description of Wall Motion for a Given Wall Motion Value*

	Lateral	Apical	Septal
Normal	>50	>60	>40
Hypokinetic	11 to 50	11 to 60	11 to 40
Akinetic	−10 to 10	−10 to 10	−10 to 10
Dyskinetic	<−10	<−10	<−10

* Modified left anterior oblique view.

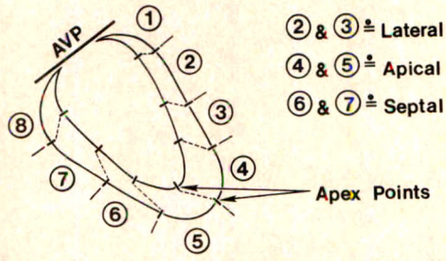


FIGURE 6. Model for measuring left ventricular wall motion from the gated blood pool scintigrams viewed in a modified left anterior oblique projection. AVP = aortic valve plane. The numbers refer to eight segments, equal in length, of the left ventricular wall. See text for details.

were defined and displayed with aortic valve planes superimposed using a Tektronix 4002-A graphics display terminal interfaced with a DEC PDP-8I minicomputer. A mapping of contraction from the diastolic boundary to the systolic boundary was accomplished with an algorithm implemented on the PDP-8I minicomputer. Essentially, each boundary was divided at the apex into two parts. These two parts, for each boundary, were further subdivided into four segments of equal length. Each segment (eight to a boundary) (Fig. 6) consists of a minimum of 16 equispaced points; corresponding systolic and diastolic segments contain the same number of points. The model assumes that each point of the diastolic boundary maps or contracts into the corresponding point of the systolic boundary; that is, the diastolic apex point maps into the systolic apex point, and so forth. The distance between each set of corresponding points is calculated and, for any given segment, these distances are averaged to give an absolute value of wall motion for that segment. These absolute values are normalized by dividing by the end-diastolic boundary length. Because this quotient is always less than 1, the normalized values are multiplied by a constant that translates the wall motion values to a desired range. The same constant is applied to all patients. The figure representing wall motion has no dimension and is not a percentage.

The distinction between normal and abnormal wall motion values was determined empirically from 10 patients with and without heart disease studied angiographically and scintigraphically at this institution. Abnormal values are categorized as shown in Table II. Segments one and eight shown in Figure 4 were not included in the analysis because of difficulty in delineating the ventricular boundary precisely in these regions.

Results

Exercise electrocardiographic responses: Twenty-seven patients underwent submaximal exercise at the time of hospital discharge after acute myocardial

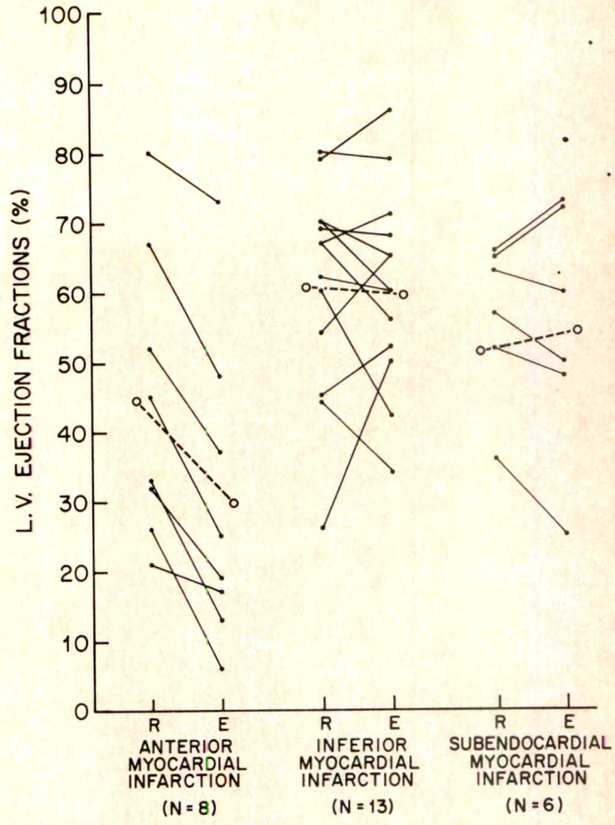


FIGURE 7. Changes in left ventricular (LV) ejection fraction between rest (R) and submaximal exercise (E) in patients with anterior, inferior and subendocardial infarcts. Note that patients with an anterior infarct manifest a marked reduction in ejection fraction with submaximal exercise, but those with an inferior or nontransmural infarct usually maintain a more stable ejection fraction with the same stress. The **open circles** and **dotted lines** in each group represent the mean rest and exercise ejection fraction for that particular group.

infarction (Table III). These patients had a mean heart rate of 74 ± 10 beats/min at rest before exercise and a rate of 106 ± 14 beats/min after exercise. Exercise testing was terminated in nine patients when they reached a heart rate of 120 to 125 beats/min (Table III) because this was the desired end point of the test. Heart rate (HR) increased significantly with exercise in patients with subendocardial infarction ($\Delta HR = 31.7$, $P < 0.005$), anterior ($\Delta HR = 33.4$, $P < 0.001$) and inferior infarction ($\Delta HR = 30.8$, $P < 0.001$), and in all patients as a group ($\Delta HR = 31.8$, $P < 0.001$). Three of these patients had a positive electrocardiographic response at this exercise level. Eleven patients achieved a heart rate of 100 to 120 beats/min; in these, the submaximal exercise test was terminated because of angina (three patients), fatigue (five patients), a positive electrocardiographic response (two patients) or arrhythmia (one patient) (Table III). In the latter patient (Case 15), left ventricular ejection fraction and segmental wall motion were measured before the development of the arrhythmia at a heart rate of approximately 105 beats/min. Six of the remaining seven patients reached a heart

TABLE III

Characteristics of Patient Population

Case no.	Age (yr) & Sex	Days After Admission	Restudied	Diagnosis	CHF	Med	MHR (E)	ECG (E)	Chest Pain	Fatigue	Arrhythmia
1	68 M	13	6 wk	Ap-lat TMI	x	Digoxin	100	(−)		x	
2	73 F	26		Ant-lat TMI	x	Digoxin	111	(−)		x	
3	59 M	17	6 wk	Ant-lat TMI	x	Digoxin, furosemide	110	(+)	x		
4	68 M	14	6 wk	Ant-lat TMI	x	Digoxin, furosemide	100	(−)		x	
5	57 M	37		Ap TMI	x	Digoxin	88	(+)*			
6	47 M	20		Ant-lat TMI	x	Digoxin	125	(−)			
7	60 M	18		Ant-lat TMI		TNG	125	(+)			
8	41 M	20		Ant-lat TMI		Quinidine, propranolol	93	(+)*			
9	77 F	19		Inf-post TMI	x	Digoxin, furosemide, isordil	107	(−)	x		
10	63 F	13	6 wk	Inf TMI		Aldomet® Esidrex®	120	(+)			
11	63 M	20	6 wk	Inf TMI		TNG	120	(−)			
12	46 M	16		Inf TMI			110	(−)		x	
13	45 M	15	6 wk	Inf TMI		Quinidine, diazepam	104	(−)	x		Junctional PVCs
14	47 M	19		Inf TMI		Isordil®	100	(−)		x	Occasional PVCs
15	55 F	12		Inf TMI			90	(−)		x	
16	56 M	13		Inf-post TMI		Furosemide	120	(−)			
17	56 M	21		Inf TMI		Quinidine, procainamide	105	(+)			Tach 150/min, VT or SVT with aberrant conduction
18	64 M	14		Inf TMI		Isordil®, propranolol	125	(+)			
19	73 F	15	7 wk	Inf-lat TMI			120	(−)			
20	50 M	14		Inf-lat TMI	x	Digoxin	94	(−)	x		
21	79 M	20		Inf-lat TMI	x	Digoxin, furosemide	100	(+)*			
22	89 M	16		Ant SEMI	x		110	(+)*			Occasional
23	48 M	14		Ant SEMI			120	(−)			
24	68 F	15		SEMI		TNG	92	(−)		x	
25	65 F	33	6 wk	Inf-lat SEMI			68	(−)	x		
26	40 M	22	7 wk	Inf-lat SEMI			90	(−)		x	
27	44 F	13		Ant SEMI			120	(−)			

* Exercise testing stopped because of positive electrocardiographic response.
− = negative electrocardiographic response; + = positive electrocardiographic response; x = symptom developed.
Ant = anterior; Ap = apical; CHF = congestive heart failure; E = on exercise testing; ECG = electrocardiographic response; Inf = inferior; Lat

rate of 90 to 100 beats/min. In these patients, the test was discontinued because of angina (one patient), fatigue (three patients) or a positive electrocardiographic response (two patients) (Table III). The remaining patient (Case 25, inferolateral myocardial infarct) had a resting heart rate of 55 beats/min and had chest pain at the initial low exercise load at a heart rate of 68 beats/min (Table III).

Ejection fraction with exercise: Patients with an anterior myocardial infarct had a mean left ventricular ejection fraction at rest (44 ± 7.3 [standard error]) that was significantly lower ($P < 0.01$) than that in patients with an inferior (61 ± 3.8) or a subendocardial (52 ± 9.4) myocardial infarct. Six of the eight patients with an anterior myocardial infarct had heart failure as a complication. With exercise, left ventricular ejection fraction decreased considerably in seven of eight patients with an anterior infarct, but did not significantly change in patients with an inferior or a subendocardial infarct (Fig. 7).

Segmental wall motion abnormality with exercise: Of the eight patients with an anterior infarct, seven had segmental wall motion abnormalities at rest (Table II). On exercise, these abnormalities were more severe in four patients (Fig. 2) and unchanged in three (Table III). The remaining patient had no wall motion abnormality at rest or during exercise. Of these eight patients, four had classic exercise electrocardiographic alterations

TABLE III
(continued)

Case no.	Ejection Fraction (%) R	E	LV Wall Motion R	E	Rest Lat	Ap	Sept	Exercise Lat	Ap	Sept	RAO
1	45	25	Diffuse hypokinesia	No changes	30	26	27	36	27	29	N.O.
2	52	37	Akinesia, ap	Dyskinesia, ap							N.O.
3	26	6	Diffuse hypokinesia	No changes	25	20	16	15	12	11	Diffuse hypokinesia
4	33	13	Hypokinesia, ap-lat	Dyskinesia, ap	30	42	69	35	21	28	Dyskinesia, ant-ap
5	32	19	Hypokinesia, ap-sept	Diffuse hypokinesia	43	41	18	27	13	15	Severe hypokinesia
6	21	17	Hypokinesia, ap-sept	No changes							Dyskinesia, ant-ap
7	80	73	Normal	Normal							
8	67	48	Akinesia, ap	Dyskinesia, ap							
9	45	52	Normal	Dyskinesia, ap	67	52	64	77	−39	36	N.O.
10	69	68	Normal	Normal	104	181	124	103	133	110	N.O.
11	54	65	Normal	Normal	90	85	69	101	146	101	N.O.
12	70	60	Normal	Normal	76	139	89	93	132	91	N.O.
13	44	34	Normal	Hypokinesia, ap	60	83	41	42	48	53	Akinesia, inf
14	62	60	Normal	Normal	99	148	91	88	132	83	N.O.
15	80	79	Normal	Normal	93	68	91	106	124	40	Normal
16	70	65	Normal	Normal							Akinesia, inf
17	67	71	Normal	Normal							Normal
18	67	56	Normal	Normal							Normal
19	79	86	Normal	Normal	134	195	127	149	246	134	N.O.
20	26	50	Akinesia, ap	No changes	45	7	41	40	−1	32	N.O.
21	60	42	Hypokinesia, sept	Akinesia, ap-sept							Akinesia, inf
22	63	60	Akinesia, ap	No changes	60	36	90	70	26	70	N.O.
23	36	25	Dyskinesia, ap	No changes	51	−16	41	51	−26	40	Dyskinesia, ant-ap
24	52	48	Normal	Normal	56	82	36	60	99	92	Normal
25	57	50	Normal	Normal	80	92	74	55	93	55	N.O.
26	66	73	Normal	Normal	98	116	97	101	147	79	Normal
27	65	72	Normal	Akinesia							Normal

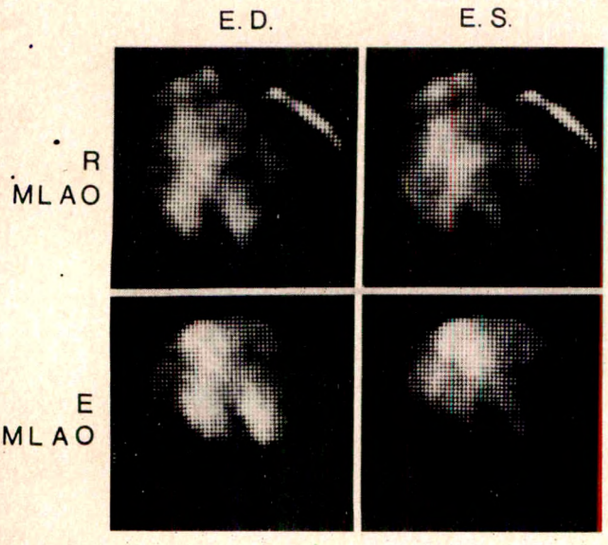
= lateral; LV = left ventricular; Med = medication; MHR = maximal heart rate; N.O. = not obtained; post = posterior; PVCs = premature ventricular complexes; R = at rest; RAO = right anterior oblique view; SEMI = subendocardial myocardial infarct; sept = septal; SVT = supraventricular tachycardia; Tach = tachycardia; TMI = transmural myocardial infarction; TNG = nitroglycerin; VT = ventricular tachycardia.

of ischemia at the end of the submaximal test (two of these patients were taking digoxin) (Table III). Of these four, two (Cases 5 and 8) had more marked wall motion abnormalities with exercise (Fig. 2), one (Case 3) had a wall motion abnormality at rest that was unchanged with exercise and the other (Case 7) had no wall motion abnormality at rest or during exercise (Table III).

Of the 13 patients with an acute inferior infarct, 11 had apparently normal segmental wall motion in the modified left anterior oblique projection at rest (Table III). Two of these 11 patients had segmental wall motion abnormalities with exercise (Table III) (Fig. 3). The two remaining patients had segmental wall motion abnormalities at rest that became more marked with submaximal exercise in one and were unchanged with exercise in one. Four of the 13 patients had a positive electrocardiographic response with submaximal exercise (one was taking digoxin) (Table III). Three showed ST-T changes at the site of the previous infarct and the fourth manifested ST-T changes in the high lateral wall and aVL. One of these patients had a more severe segmental wall motion abnormality with exercise (Table III).

Of the six patients with a nontransmural myocardial infarct, four had no identifiable abnormality of left ventricular segmental wall motion at rest (Table III). Only two of these four manifested a segmental wall motion abnormality with exercise (Table III) (Fig. 8). The remaining two patients had a segmental wall motion abnormality at rest, but no exaggeration of that abnormality or new regional abnormality developed with submaximal exercise (Table III). One of these two patients had a positive electrocardiographic ischemic response with exercise. This patient had a left ventricular segmental wall motion abnormality at rest that did not change with exercise (Table III).

Correlation of right and modified left anterior oblique views: Radionuclide gated blood pool scintigrams obtained at rest in the right anterior oblique projection were available in 14 patients. Four had an anterior transmural, six an inferior transmural and four a nontransmural myocardial infarct. The correlation



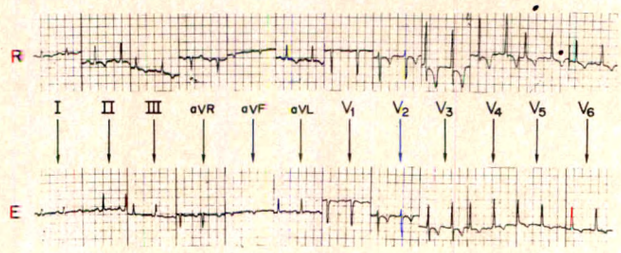


FIGURE 8. Case 27 (Table III). **Left,** gated scintigrams obtained from a patient with subendocardial myocardial infarction showing normal left ventricular wall motion at rest and apical akinesia with submaxial exercise. Abbreviations as in Figure 1. **Right,** electrocardiogram at rest (R) and negative electrocardiographic response obtained during exercise (E) in the same patient.

between the right anterior oblique and modified left anterior oblique views in identifying segmental wall motion abnormalities was excellent in those patients with an anterior transmural or a nontransmural infarct (Table III). However, in three patients with an inferior infarct, ventricular segmental wall motion abnormalities at rest were evident in the right anterior oblique view but not in the left anterior oblique projection (Table III).

Repeat studies: Nine patients were studied again 6 weeks after the first submaximal exercise evaluation (Table IV). None had experienced an important ischemic event since the initial evaluation. No patient attained a heart rate appreciably higher than that achieved during the initial exercise test. Six of the nine had the same segmental wall motion response to exercise demonstrated during the initial study (Table IV). There was no major group difference in the alterations in left ventricular ejection fraction or the electrocardiographic response with exercise compared with values noted during the initial exercise test (Table IV).

Discussion

Comparison of results of dynamic myocardial scintigraphy in anterior, inferior and transmural myocardial infarction: Our study evaluated the ability of dynamic myocardial scintigraphy and electrocardiographic monitoring to detect myocardial ischemia in patients undergoing submaximal exercise 2 1/2 to 3 weeks after acute myocardial infarction. The data demonstrate that patients with a recent acute anterior infarction generally manifest a marked reduction in left ventricular ejection fraction with submaximal exercise (Fig. 7). The majority of these patients have detectable segmental wall motion abnormalities at rest that, in some, become even more marked with minimal effort. Electrocardiographic testing did not identify ischemic responses in some of these patients and, as expected, did not identify the marked impairment of left ventricular function developing with modest effort. In contrast, patients with inferior and nontransmural infarction had no significant reduction in left ventricular ejection fraction (Fig. 7). Patients with an acute inferior infarct whose scintigraphic images were obtained in the modified left anterior oblique projection infrequently manifested regional left ventricular wall motion abnormalities at rest and also generally failed to show wall motion abnormalities with exercise. However, these findings may have been partly the result of the imaging projection utilized because three of these six patients had evidence of wall motion abnormalities at rest in the right anterior oblique projection. Three of six patients with a nontransmural infarct also manifested regional wall motion abnormalities during exercise. The relatively stable left ventricular ejection fraction during exercise in patients with an inferior infarct does not appear to be primarily related to an undetected inferior wall motion abnormality because one would not expect the wall motion abnormality in these patients to be severe. However, this possibility cannot be absolutely excluded. Patients with a nontransmural infarct also did not have a significantly reduced ejection fraction with exercise. Patients with an inferior infarct more often manifested a positive electrocardiographic response than segmental wall motion abnormalities, but this also may have been due to use of a modified left anterior rather than the right anterior oblique projection.

Previous studies: Green, Borer, Kent and their coworkers[6,14,15] showed that dynamic myocardial scintigraphy with maximal exercise testing utilizing technetium-labeled albumin is useful in identifying ventricular wall motion abnormalities in patients with chronic ischemic heart disease,[6] assessing the influence of coronary artery revascularization on segmental wall motion[14] and helping to identify left ventricular function abnormalities in patients with aortic regurgita-

TABLE IV

Repeat Submaximal Exercise Testing in Nine Patients 6 Weeks After Myocardial Infarct

Case no.	Age (yr) & sex	Exercise Test*	Diagnosis	CHF	Med	MHR (E)	ECG (E)	Chest pain	Fatigue	LV Ejection Fraction Rest	LV Ejection Fraction Exercise	LV Wall Motion R	LV Wall Motion E
1	68 M	1 (13 days)*	Ap-lat TMI	x	Digoxin, Lasix®	100	(−)		x	45	25	Diffuse hypokinesia	No changes
		2 (6 wk)			Same drugs	100	(−)		x	47	39	Apical akinesia	Ap dyskinesia
6	59 M	1 (17 days)	Ant-lat TMI	x	Digoxin, Lasix®	110	(+)	x		26	6	Severe diffuse hypokinesia	No changes
		2 (6 wk)		x	Same drugs	110	(+)	x		16	14	Severe diffuse hypokinesia	No changes
4	68 M	1 (14 days)	Ant-lat TMI	x	Digoxin, Lasix®	100	(−)		x	33	13	Hypokinesia, ap-lat	Ap dyskinesia
		2 (6 wk)			Same drugs	88	(+)	x		36	44	Hypokinesia, ap-lat	Ap dyskinesia
10	63 F	1 (13 days)	Inf TMI		None	120	(+)			69	68	Normal	No changes
		2 (6 wk)				120	(−)		x	57	65	Normal	No changes
11	63 M	1 (20 days)	Inf TMI		TNG	120	(−)			54	65	Normal	No changes
		2 (6 wk)				136	(−)		x	61	61	Normal	No changes
13	45 M	1 (15 days)	Inf TMI		None	104	(−)	x		44	34	Normal	Ap hypokinesia
		2 (6 wk)				125	(+)		x	32	20	Severe hypokinesia	No changes
19	73 F	1 (15 days)	Inf-lat TMI		None	120	(−)			79	86	Normal	No changes
		2 (7 wk)				110	(−)		x	79	79	Normal	No changes
25	65 F	1 (33 days)	Inf-lat SEMI		Isordil®	68	(−)	x		57	50	Normal	No changes
		2 (6 wk)			Isordil®	76	(−)		x	53	49	Lateral akinesia	Lat dyskinesia
26	40 M	1 (22 days)	Inf-lat SEMI		None	90	(−)		x	66	73	Normal	No changes
		2 (7 wk)				115	(−)		x	63	74	Normal	No changes

* 1 and 2 indicate first and second submaximal exercise tests. Data in parentheses indicate the number of days after admission (test 1) or weeks after infarction (test 2) the test was performed.
Abbreviations as in Table III.

tion.[15] These investigators emphasized that with normal persons, left ventricular ejection fraction increases with exercise, but in those with extensive coronary artery disease ejection fraction may decrease with maximal exercise.[6] Borer et al.[6] also found that the left anterior oblique imaging projection fails to identify segmental wall motion abnormalities in some patients with right coronary artery disease.[6] The modified left anterior oblique imaging projection allows one to separate the left and right ventricles, thus eliminating overlapping right ventricle as one analyzes segmental left ventricular wall motion. However, it is not the optimal way to image scintigraphically the diaphragmatic aspect of the left ventricle.

Advantages and reproducibility of method: The technique utilized in this study to obtain stable radionuclide blood pool scintigrams is a modification of the method for in vivo labeling of red blood cells that we[10] have previously described. The modification allows one to obtain stable blood pool scintigrams within 20 minutes after completing an initial intravenous injection of 5 mg of stannous pyrophosphate followed within 10 to 15 minutes by the intravenous injection of 15 mCi of technetium-99m pertechnetate. In patients who had left heart catheterization, angiographic and scintigraphic measurements of left venticular ejection fraction and segmental wall motion correlated well (Table I) (Fig. 4 and 5).

A potential concern in the acquisition of gated scintigraphic exercise studies is one's capability to collect enough radionuclide counts to define ventricular boundaries accurately. At the higher work loads some patients are not able to exercise long enough to allow accurate left ventricular definition. In these patients we utilized the last exercise level reached that resulted in a sufficient number of radionuclide counts permitting delineation of left ventricular boundaries and thus analysis of left ventricular ejection fraction and segmental wall motion. Increased data acquisition rates will become possible as a result of further development of imaging cameras and computer systems. Consequently, this form of scintigraphic exercise testing should be even more useful in identifying ischemic responses and alterations in cardiac function in patients with heart disease.

Our exercise scintigraphic results appeared to be reproducible. The nine patients undergoing repeat submaximal exercise testing 6 weeks after hospital discharge had left ventricular ejection fraction and segmental wall motion responses similar to those of the initial submaximal test before discharge.

Clinical implications: Our results demonstrate that, optimally, both dynamic myocardial scintigraphy and electrocardiographic monitoring should be used to identify ischemic responses in patients undergoing submaximal exercise 2 1/2 to 3 weeks after myocardial infarction. The data also suggest that patients with an anterior infarct have a different functional response to submaximal exercise from patients with an inferior or nontransmural infarct. The prognostic importance of the different left ventricular functional responses and patterns of regional wall motion alteration will have to be determined in future studies of larger numbers of patients evaluated after myocardial infarction.

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References

1. **Detry JMR:** Exercise Testing and Training in Coronary Heart Disease, Baltimore, Willimas & Wilkins, 1973
2. **Froelicher VF, Thompson AF, Longo MR, et al:** Value of exercise testing for screening asymptomatic men for latent coronary artery disease. Prog Cardiovasc Dis 18:265–276, 1976
3. **Bruce RA, Hornstein T, Backman J:** Myocardial infarction after normal response to maximal exercise. Circulation 38:552–558, 1968
4. **McHenry PL, Cogan OJ, Elliott WC, et al:** False-positive ECG response to exercise secondary to hyperventilation. Cineangiographic correlation. Am Heart J 79:683–687, 1970
5. **Green MV, Ostrow HG, Douglas MA, et al:** High temporal resolution ECG-gated scintigraphic angiocardiography. J Nucl Med 16:95–98, 1975
6. **Borer JS, Bacharach SL, Green MV, et al:** Radionuclide cineangiography of cardiac function during exercise. N Engl J Med 296:839–844, 1977
7. **Willerson JT, Stone MJ, Ting R, et al:** Radioimmunoassay of creatine kinase-B isoenzyme in human sera: results in patients with acute mhocardial infarction. Proc Natl Acad Sci USA 74:1711–1715, 1977
8. **Willerson JT, Parkey RW, Bonte FJ, et al:** Technetium stannous pyrophosphate myocardial scintigrams in patients with chest pain of varying etiology. Circulation 51:1046–1052, 1975
9. **Wohl AJ, Lewis HR, Campbell W, et al:** Cardiovascular function during early recovery from acute myocardial infarction. Circulation, 56:931–937, 1977
10. **Stokely EM, Parkey RW, Bonte FJ, et al:** Gated blood pool imaging following technetium-99m phosphate scintigraphy. Radiology 120:433–434, 1976
11. **Strauss HW, Zaret BL, Hurley PJ, et al:** A scintigraphic method for measuring left ventricular ejection fraction in man without cardiac catheterization. Am J Cardiol 28:575–580, 1971
12. **Dodge HT, Sandler H, Baxley WA, et al:** Usefulness and limitations of radiographic methods for determining left ventricular volume. Am J Cardiol 18:10–234, 1966
13. **Alderson PO, Bernier DR, Ludbrook PA, et al:** Serial radionuclide determinations of the ejection fraction with ^{99m}Tc-labeled red blood cells. Radiology 119:729–730, 1976
14. **Kent KM, Borer JS, Green MV, et al:** Effects of coronary artery bypass operation on global and regional left ventricular function during exercise (abstr). Clin Res 25:230A, 1977
15. **Borer JS, Bacharach SL, Green MW, et al:** Exercise induced left ventricular dysfunction in symptomatic and asymptomatic patients with severe aortic regurgitation assessed by radionuclide angiography (abstr). Am J Cardiol 39:284, 1977

Comparison of S-T Segment Changes on Exercise Testing With Angiographic Findings in Patients With Prior Myocardial Infarction

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Ninety-seven patients with a prior transmural myocardial infarction who underwent coronary angiography and treadmill stress testing were studied retrospectively to assess the reliability of the exercise electrocardiogram in detecting additional disease in patients with a prior infarction. In patients with a previous inferior wall infarction, the S-T response to the treadmill stress test had a high degree of sensitivity (87 percent) and specificity (90 percent) in detecting additional significant coronary artery disease. However, in patients with a previous anteroseptal wall infarction, the S-T response had much less sensitivity (52 percent), but the degree of specificity remained high (90 percent). In this group a positive test suggested the presence of ischemia in the lateral or inferoposterior region of the myocardium, or both. A negative S-T response was of little value in distinguishing among groups of patients with single or multiple vessel coronary artery disease. The presence of an anterior ventricular aneurysm is most likely responsible for this low sensitivity rate because it generates an opposing force to the ischemic vector, thereby cancelling the S-T segment changes and producing a false negative treadmill stress test. The resting surface electrocardiogram proved useful in predicting a false negative exercise test. The presence of Q waves in the precordial leads extending to lead V_4 or beyond decreased the sensitivity rate of treadmill stress testing to 33 percent.

Stress testing is a valuable noninvasive method of assessing the presence of underlying coronary disease. It is apparent that the number and location of significantly narrowed vessels are important determinants of morbidity and mortality.[1] Patients who have had a previous myocardial infarction may or may not be at risk of infarction in other areas of the myocardium depending on the presence or absence of additional disease. Therefore it is important to determine the usefulness of stress testing after a myocardial infarction.

To date, studies correlating the sensitivity and specificity of the treadmill stress test in patients with a previous myocardial infarction suggest that the sensitivity is reduced.[2–5] This study was undertaken to determine the reliability of the treadmill stress test in detecting other areas of coronary artery disease in patients with a previous inferior wall myocardial infarction or previous anteroseptal wall myocardial infarction, or both.

Methods

Selection of patients: All patient treadmill stress test records performed at this center since 1972 were reviewed retrospectively. There were 97 patients with myocardial infarction who had had coronary angiography and treadmill stress testing. All available information, including the hospital records, was reviewed. The criterion for selection was a previous transmural myocardial infarction as

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demonstrated by significant Q waves in the resting electrocardiogram permitting the area of infarction to be localized to either the inferior or the anteroseptal area.[6] All patients had a clinical history of myocardial infarction at least 2 months before the treadmill stress test. The treadmill stress test and coronary angiography were performed within 5 months of each other. All patients were symptomatic and were suspected of having further coronary artery disease necessitating coronary angiography. Patients with pericarditis, valvular heart disease or congenital heart disease were excluded. Also excluded were patients with severe hypertension or primary myocardial disease and those who had been taking digitalis before the treadmill stress test.

Exercise test: Patients underwent maximal exercise according to the Ellestad protocol.[7,8] A three lead system of recording the electrocardiogram was used in 80 of the 97 patients. These leads consisted of a bipolar CM_5 lead, a vertical bipolar lead III and a unipolar V_1 lead.[8] The remaining 17 patients had a single CM_5 lead recording. Each lead was evaluated for significant S-T depression defined as depression below the resting level of 1.0 mm 60 msec from the J point if the segment was horizontal or flat and 1.5 mm 80 msec from the J point if the segment was upsloping during exercise or in the immediate postexercise period.[8,9] Each lead was also examined for significant S-T elevation defined as 1.0 mm above the resting level during exercise or immediately after. The treadmill stress test was examined independently without prior knowledge of the coronary angiograms.

For the purposes of our study, a true positive test was defined as one showing significant S-T depression in a patient who had coronary obstruction to an area of myocardium that had not undergone infarction as well as obstruction in a vessel perfusing the area of infarcted myocardium. A true negative test was defined as one showing no S-T depression in a subject who had disease only in the vessels perfusing the area of infarcted myocardium.

Cardiac catheterization: This procedure was performed with the Sones or Judkins technique. Cineangiograms were recorded on 35 mm film in multiple views. The coronary obstructions were then classified according to severity into six groups (0 to 19 percent, 20 to 50 percent, 51 to 70 percent, 71 to 89 percent, 90 to 99 percent and 100 percent). The degree of obstruction was determined by measuring the obstructed area and subtracting the ratio of the square of the obstructed diameter over the square of the unobstructed diameter from 100 percent; that is, percent obstruction = 100 percent − [(obstructed diameter)^2 divided by (unobstructed diameter)^2]. For the purpose of this study, a luminal stenosis of 50 percent or greater corresponding to a 70 percent or greater cross-sectional area of obstruction was considered significant. Single plane left ventricular cineangiography was performed in the right anterior oblique projection. The presence of collateral channels was noted and tabulated.

TABLE I

Left Ventricular Contraction Abnormalities in 47 Patients With Inferior Wall Infarction

Site of Infarct	Dyskinesia	Akinesia	Hypokinesia	Normal	Total
Inf	4	23	14	6	47
Ap	8	15	14	10	47
Ant	0	1	13	33	47

Ant = anterior wall; Ap = apical wall; Inf = inferior wall.

Each cineangiogram was reviewed and the vessel or vessels that supplied the anteroseptal region, the lateral wall region or the inferior wall region were noted. The degree of obstruction and presence of collateral vessels to the respective areas were tabulated. The inferior wall was supplied by the right coronary artery or the left circumflex coronary artery and the lateral wall by the marginal circumflex branch, an intermediate vessel or the diagonal branch of the left anterior descending artery, alone or in combination. The anteroseptal region was considered supplied by the left anterior descending artery with or without significant contribution from the diagonal artery.

The left ventricle was divided into five segments as follows: posterobasal, diaphragmatic, apical, anterolateral and anterobasal. Areas with an abnormal contraction pattern were described qualitatively as hypokinetic when systolic movement was less than normal, akinetic when no inward movement was observed during systole and dyskinetic when a paradoxical systolic movement was seen.[6] An aneurysm was defined as a dyskinetic area. A small aneurysm comprised dyskinesia of one segment, a medium-sized aneurysm dyskinesia of two segments and a large aneurysm dyskinesia of three or more segments of the myocardium. The coronary angiograms and left ventricular angiograms were graded without prior knowledge of results of the treadmill stress test.

Electrocardiogram: The resting electrocardiograms of all patients were reviewed. The patients were grouped into those with inferior wall infarction, anteroseptal wall infarction or anteroseptal plus inferior wall infarction.[6] In addition, the 33 patients with an anteroseptal infarction and additional coronary artery disease were separated into three groups according to the extent of significant Q waves in the precordial leads. These groups included 10 patients with Q waves in leads V_1 to V_4 or beyond, 10 patients with Q waves in leads V_1 to V_3 and 13 patients with Q waves in only one or two precordial leads.

Results

A total of 99 cineangiograms and treadmill stress tests were reviewed in 97 patients (2 patients were studied twice). There were 86 men and 11 women ranging in age from 30 to 74 years (average age 54). There were 47 patients with inferior infarction, 43 with anteroseptal infarction and 9 with both anteroseptal and inferior infarctions. The time interval from infarction to treadmill stress testing ranged from 2 months to 14 years (mean 33 months). The interval between treadmill stress testing and coronary angiography ranged from a few hours to 5 months (average 20 days).

Inferior Myocardial Infarction

Correlation of infarction with left ventricular angiogram: Of the 47 patients with an inferior infarction, 45 had evidence of contraction abnormalities in the left ventricular angiogram (Table I). The angiograms were classified according to the most severe abnormality demonstrated in the anterior, inferior or apical segment. There were 41 angiograms with inferior wall contraction abnormalities (23 akinetic, 4 dyskinetic and 14 hypokinetic). There were 37 apical abnormalities (15 akinetic, 8 dyskinetic and 14 hypokinetic). The anterior wall was normal in 33 cases, hypokinetic in 13 and akinetic in 1 case.

TABLE II

Sensitivity and Specificity of the Treadmill Stress Test in 47 Patients With Inferior Wall Myocardial Infarction

Treadmill Stress test	No Additional Disease*	Additional Coronary Artery Disease			
		Ant-Sept	Ant & Lat	Lat	Total
Percent positive	10% (1)	70% (7)	88% (21)	100% (3)	84% (31)
Percent negative	90% (9)	30% (3)	12% (3)	0% (0)	16% (6)

* Significant coronary arterial narrowing only in the artery leading to the inferior wall.

Ant & lat = coronary arterial narrowing in the inferior, anteroseptal and lateral walls; Ant-sept = coronary arterial narrowing in both the arteries leading to the inferior and anterior septal walls; Lat = coronary arterial narrowing in the inferior and lateral walls. Figures in parentheses indicate the number of patients in each group.

TABLE III

Left Ventricular Contraction Abnormalities in 43 Patients With Anteroseptal Wall Infarction

Site of Infarct	Dyskinesia	Akinesia	Hypokinesia	Normal	Total
Inf	0	1	10	32	43
Ap	30	2	6	5	43
Ant	10	11	14	8	43

Abbreviations as in Table I.

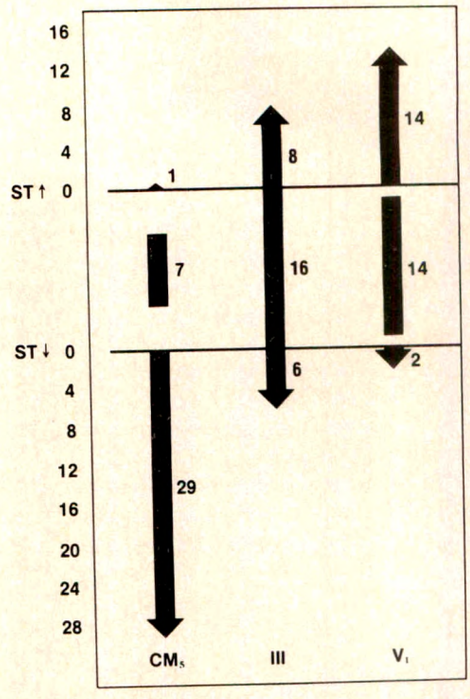

FIGURE 1. S-T changes noted during the treadmill stress testing in each of the three leads (CM_5, III and V_1) in patients with myocardial infarction and additional coronary artery disease. The **arrows pointing down** represent the number of patients with significant S-T depression. The **arrows pointing up** indicate the number of patients with significant S-T elevation. The middle bars indicate the number with S-T changes of less than 1 mm. The **numbers** on the **ordinate** and to the **right of each arrow or bar** represent the number of patients in each group.

Correlation of stress test with coronary angiogram: There were 37 patients with a previous inferior infarction who had significant additional disease in the coronary artery leading to either the anteroseptal wall or the lateral wall, or both. These patients, therefore, not only had significant coronary obstruction leading to the area of the inferior wall infarction, but also showed significant coronary obstruction to an additional area of the heart.

Thirty-one patients (84 percent) had significant S-T depression on treadmill testing (true positive tests); six patients (16 percent) had no S-T depression (false negative tests). Anteroseptal ischemia was detected with the treadmill test in 7 of 10 patients, lateral wall ischemia in 3 of 3 patients and combined lateral and anteroseptal wall ischemia in 21 of 24 patients (88 percent).

Ten patients had no additional coronary disease other than that leading to the area of inferior wall infarction. Nine of the 10 patients had a negative S-T response on exercise (true negative test). The one patient with a positive response had a subsequent single vessel bypass to the right coronary artery.

In patients with a previous inferior infarction, a positive treadmill stress test response had a sensitivity rate of 84 percent. A negative treadmill stress test response had a specificity rate of 90 percent (Table II).

Stress test lead pattern: Figure 1 shows the relation between the S-T changes produced on treadmill testing in the three leads recorded in the patients with additional coronary disease. The CM_5 lead was the most sensitive lead for detecting ischemia, showing S-T depression in 29 patients, no S-T change in 7 and S-T elevation in 1 patient. Leads V_1 and III were recorded in 31 of these patients. Lead V_1 showed either no S-T change (14 patients) or reciprocal S-T depression (14 patients). Two patients had S-T depression detected in lead V_1 only. Lead III showed no S-T change in 16 of the 31 patients, S-T depression in 6 and S-T elevation in 8.

Anteroseptal Myocardial Infarction

Correlation of infarction with left ventricular angiogram: Forty-one of the 43 patients with electrocardiographic evidence of an anteroseptal infarct had evidence of contraction abnormalities in the left ventricular angiogram. The angiograms were again classified according to the most severe segmental abnormality (Table III). There were 35 anterior wall abnormalities (11 akinetic, 10 dyskinetic and 14 hypokinetic) and 38 apical contraction abnormalities (30 dyskinetic, 2 akinetic and 6 hypokinetic). The inferior wall was normal in 32 patients, hypokinetic in 10 and akinetic in 1.

Correlation of stress test with coronary angiogram: There were 33 patients with a previous anteroseptal infarct and additional significant coronary artery

disease. Seventeen (52 percent) of these 33 had a positive S-T response on treadmill stress testing (true positive test) and 16 (48 percent) had a false negative S-T response. Lateral wall ischemia was detected in 4 of 6 patients, inferior wall ischemia in 5 of 7 and combined lateral and inferior wall ischemia in 8 of 20.

Ten patients had no additional coronary disease, and nine of these had a true negative treadmill stress test response. The patient with a false positive response subsequently had bypass surgery to the left anterior descending coronary artery, but was again classified as having a false positive response for the purpose of this study.

In patients with a previous anteroseptal infarction, a positive stress test response had a sensitivity rate of 52 percent and a negative response had a specificity rate of 90 percent (Table IV).

Resting electrocardiogram: The resting electrocardiogram was compared with treadmill stress test responses in the 33 patients with anteroseptal infarction and additional significant coronary disease. The incidence rate of a false negative stress test was 70 percent in 10 patients who had Q waves in leads V_1 to V_4 or beyond, 31 percent in 13 patients with Q waves in one or two precordial leads and 50 percent in the remaining 10 patients with Q waves in leads V_1 to V_3.

Stress test lead pattern: Figure 2 demonstrates the relation between S-T changes on treadmill testing in the three leads recorded in the 33 patients with additional coronary disease. Multiple lead recordings were available in 28 of these patients. Also included is the relation between electrocardiographic changes and the presence of two or more segments of dyskinesia versus only one segment or none. The exercise electrocardiogram was not a sensitive detector of further coronary artery disease in this group of patients. In 16 of the 33 patients the CM_5 lead revealed either no change in S-T segment or S-T elevation (false negative response). S-T elevation in this lead was associated with a large apical anterior wall aneurysm with or without further coronary disease in all eight patients with this finding (Fig. 3). In 14 of 16 the patients (93 percent) with a false negative treadmill test response, two or more segments of dyskinesia of the apical-anterior wall were demonstrated on left ventricular angiography.

Among the 28 patients with additional coronary artery disease and a previous anteroseptal infarct, lead V_1 showed no S-T change in 18 and S-T elevation in the remaining 10 (Fig. 4). Analysis of S-T elevation in this lead in all patients with an anteroseptal infarct, irrespective of additional disease, revealed that in 8 of 11 patients (82 percent) it was associated with inferoposterior wall coronary disease (Fig. 5). Furthermore, the fewer the number of apical-anterior segments of dyskinesia the more likely was S-T segment elevation to be present (Fig. 6). This finding suggests that exercise-induced S-T elevation in lead V_1 is related to posterior wall ischemia rather than to anterior aneurysm.

Lead III showed no S-T change in 16 of 28 patients, S-T segment depression in 5 and S-T elevation in 7.

TABLE IV

Sensitivity and Specificity of Treadmill Stress Test in 43 Patients With Anteroseptal Wall Infarction

Treadmill Stress test	No Additional Disease	Additional Coronary Artery Disease			
		Lat	Lat & Inf	Inf	Total
Percent positive	10% (1)	66% (4)	40% (8)	71% (5)	52% (17)
Percent negative	90% (9)	34% (2)	60% (12)	29% (2)	48% (16)

Inf = inferior; other abbreviations as in Table II.

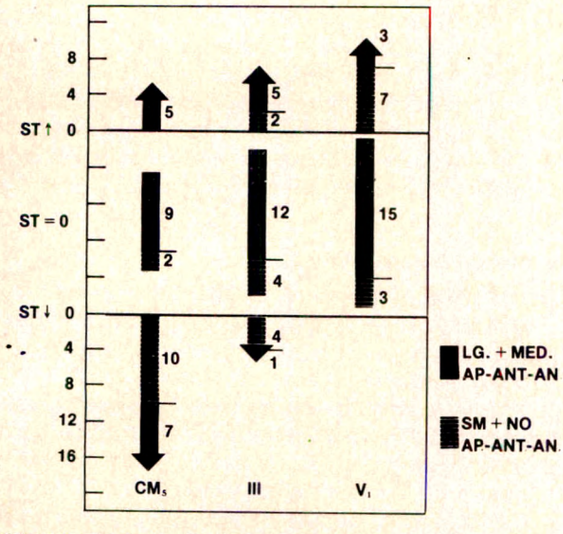

FIGURE 2. S-T changes noted during the stress test in each of the three leads (CM_5, III and V_1) in patients with an anteroseptal myocardial infarction and additional coronary artery disease. Conventions as in Figure 1. Note that the presence of a medium (MED.) or large (LG.) apical-anterior aneurysm (AP-ANT-AN) results in no S-T change or S-T elevation in lead CM_5. SM + NO = patients with a small or no apical-anterior aneurysm.

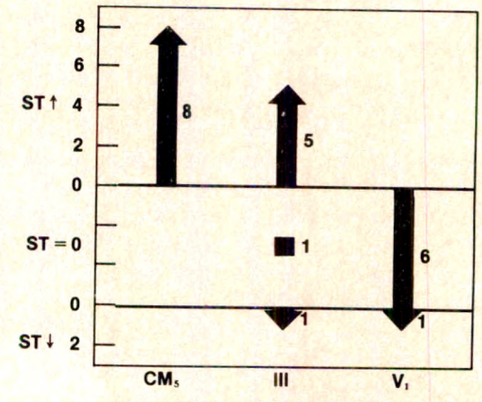

FIGURE 3. S-T changes during treadmill stress testing in all eight patients in this study who had an anteroseptal myocardial infarction and S-T elevation in lead CM_5. All eight patients had an associated large apical-anterior aneurysm. Conventions as in Figure 1.

Combined Anterior Septal and Inferior Myocardial Infarction

Nine patients had both a previous anteroseptal and a previous inferior infarction (Table V). The ventriculogram showed an inferior wall akinetic aneurysm in six of these patients, a hypokinetic inferior wall in two and a normal inferior wall in one. The ventricular apex was dyskinetic in six patients, hypokinetic in one patient and normal in the two patients. The anterior wall showed a dyskinetic segment in three patients, an akinetic segment in two, a hypokinetic segment in three and normal contraction in one patient.

Of the seven patients with combined infarction and additional coronary artery disease in the lateral wall, six had an abnormal S-T response typical of ischemia on the stress test and one had a false negative response (Table VI). The remaining two patients had no additional disease and one of them had a positive and one a negative stress test S-T response.

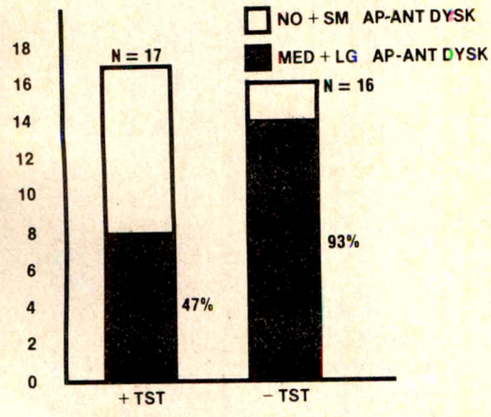

FIGURE 4. Comparison of true positive (+TST) and false negative (−TST) treadmill stress test responses in 33 patients with an anteroseptal myocardial infarction and additional coronary artery disease. Note the frequent occurrence of false negative responses. N = number of patients; NO + SM and MED + LG AP-ANT DYSK = no plus small and medium plus large apical-anterior dyskinesia.

TABLE V

Left Ventricular Contraction Abnormalities in Nine Patients With Anteroseptal Plus Inferior Wall Infarction

	Dyskinesia	Akinesia	Hypokinesia	Normal	Total
Inf	0	6	2	1	9
Ap	6	0	1	2	9
Ant	3	2	3	1	9

Abbreviations as in Table I.

TABLE VI

Sensitivity and Specificity of the Treadmill Stress Test in Nine Patients With Anteroseptal Plus Inferior Wall Infarction

Treadmill Stress Test	No Additional Disease	Lateral Wall Disease
Positive (no.)	1	6
Negative (no.)	1	1

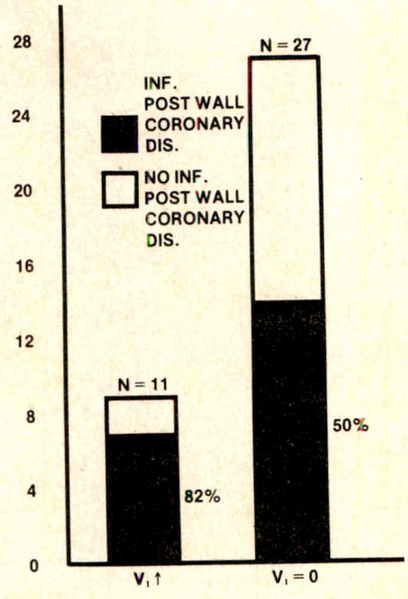

FIGURE 5. S-T changes in lead V_1 during treadmill stress testing in 28 patients with an anteroseptal myocardial infarction. S-T elevation in lead V_1 ($V_1\uparrow$) is associated with inferoposterior (INF.POST) wall coronary artery disease (DIS.). N = number of patients; 0 = no S-T change.

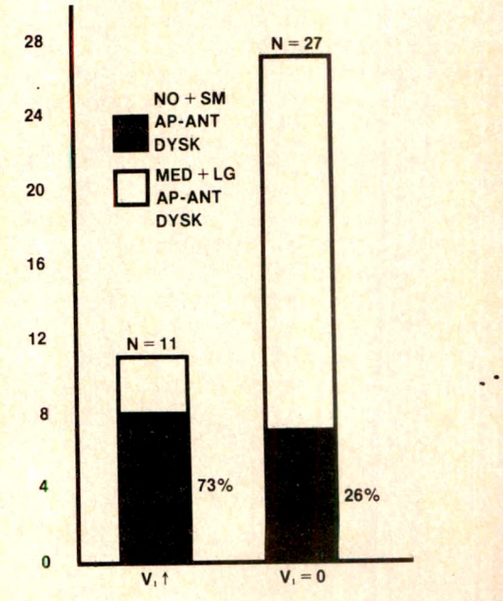

FIGURE 6. Lead V_1 changes during treadmill stress test in 28 patients with an anteroseptal myocardial infarction. S-T elevation in lead V_1 ($V_1\uparrow$) is associated with little or no apical-anterior dyskinetic aneurysm (AP-ANT DYSK). N = number of patients; 0 = no S-T change; other abbreviations as in Figure 4.

Discussion

Inferior versus anterior wall infarction: In the patients with electrocardiographic evidence of inferior wall infarction, the ventriculogram revealed contraction abnormalities predominantly limited to the inferior and apical regions of the heart. This relation was previously reported by Miller et al.[10] and others.[11] The right coronary or left circumflex artery supplies the inferoapical segment of the heart, and this pattern would be expected after occlusion of either vessel. The contraction abnormalities were less severe than in the patients with anteroseptal infarction; most patients had hypokinetic or akinetic segments, and few had dyskinetic aneurysms.

The S-T response on treadmill stress testing in the group with inferior wall infarction showed a high degree of sensitivity (84 percent) and specificity (90 percent). These rates are comparable with the best results reported by others[3,4,5,8,12,13] for stress testing in patients with or without previous myocardial damage. Thus, the treadmill stress test appears to be a valuable means of identifying further significant coronary artery disease in patients with a previous inferior infarction.

In the patients with electrocardiographic evidence of anteroseptal infarction, the ventriculogram revealed severe contraction abnormalities that were primarily dyskinetic and localized to the apical and anterior walls. These changes corresponded to the distribution of the left anterior descending artery and the expected abnormality produced by occlusion of this vessel. The extent and severity of contraction abnormalities was greater in the patients with anteroseptal infarction than in those with inferior infarcts, as previously reported.[10] The S-T response on stress testing had a low degree of sensitivity in patients with anteroseptal infarction. This finding is consistent with a previous report by Kasser and Bruce[14] that the presence of a previous infarct reduced the percent of positive S-T responses on treadmill testing.[14]

The patients with both an anteroseptal and an inferior infarction had evidence of contraction abnormalities in the anterior, apical and inferior walls. The S-T response on treadmill testing was useful in detecting lateral wall ischemia in this small group of patients but, because the group was small, no conclusions could be drawn.

The difference in the sensitivity of the S-T response of the treadmill stress test in patients with an anteroseptal wall infarction and in those with an inferior wall infarction was significant. This difference was probably related to both the size and the location of the left ventricular contraction abnormalities in the two conditions. In inferior infarction, the contraction abnormalities were located along the inferior or inferoapical region and were predominantly akinetic or hypokinetic. In this location these contraction abnormalities did not affect the ischemic S-T vector produced by the anteroapical or lateral ischemic wall.

Anteroapical dyskinetic aneurysms: effect on incidence of false negative tests: The group with anterior myocardial infarction had large anteroapical dyskinetic aneurysms. The incidence of false negative treadmill stress tests was greater in these patients than in the other groups. In our study and in those of others,[15,16] stress test-induced S-T elevation was associated with an anteroapical aneurysm. The S-T elevation generated by the aneurysm negated the S-T depression produced by exercise-induced subendocardial ischemia, resulting in an increased incidence of false negative treadmill stress tests in this group.

Miller et al.[10] reported that patients with an anteroseptal infarct tended to have a large dyskinetic anteroapical aneurysm when the resting electrocardiogram showed extension of Q waves to lead V_4 or beyond.[10] In our series, when the resting electrocardiogram showed Q waves to V_4 or beyond the incidence of false negative treadmill stress tests was much greater (70 percent) than when Q waves were present in only two precordial leads (31 percent); when there were Q waves in leads V_1 to V_3, the percent of false negative stress tests was intermediate (50 percent). These findings suggest that the resting electrocardiogram is useful in predicting which patients will be likely to have a false negative S-T response on stress testing.

Clinical implications: Our results should be interpreted with caution because of the highly selected group of patients studied. These patients were suspected of having additional coronary artery disease on clinical assessment, and the majority had multiple vessel disease. This may explain the high degree of sensitivity of the S-T response on treadmill testing in the group with inferior wall infarction. In addition, the patients were selected on the basis of having significant Q waves in the resting electrocardiogram. Only 2 of 20 patients who had single vessel disease had a positive S-T response; for the purposes of this study both responses were classified as false positive. It was clinically apparent that these patients had continued ischemia in a single area of myocardium around an infarcted zone and subsequently underwent single vessel bypass surgery. Therefore, a positive treadmill stress test does not necessarily imply multiple vessel disease. The incidence of multiple vessel disease in patients with a previously documented infarction without significant Q wave abnormalities remains to be determined.

References

1. **Bruschke AVG, Proudfit WC, Sones FM:** Progress study of 590 consecutive nonsurgical cases of coronary disease followed 5–9 years. Circulation 47:1147–1153, 1973
2. **Simoons ML, Brand M, Hugenholtz PG:** Quantitative analysis of exercise electrocardiograms and left ventricular angiograms in patients with abnormal QRS complexes at rest. Circulation 55: 55–60, 1977
3. **Cohn PF, Vokonas PS, Herman MV, et al:** Post exercise EKG in patients with abnormal resting EKGs. Circulation 43:648–654, 1971
4. **Linhart JW, Turnoff HB:** Maximum treadmill exercise test in patients with abnormal control electrocardiograms. Circulation 49:557–672, 1974
5. **Savron SV, Bryson AL, Welch TG, et al:** Clinical correlates of

coronary cineangiography in young males with myocardial infarction. Am Heart J 91:551–555, 1976
6. A reporting system on patients evaluated for coronary artery disease: Report of the Ad Hoc Committee for grading of coronary artery disease, Council on Cardiovascular Surgery, American Heart Association. Circulation 51:Suppl IV:IV-5–IV-40, 1975
7. **Ellestad MH:** Maximal treadmill stress testing for cardiovascular evaluation. Circulation 39:517–522, 1968
8. **Ellestad MH:** Stress Testing, Principles and Practice: Philadelphia, FA Davis, 1975, p 65–74
9. **Stuart RJ, Ellestad MH:** Upsloping S-T segment in exercise stress testing. Am J Cardiol 37:19–22, 1976
10. **Miller RR, Amsterdam EA, Bogren HG, et al;** Electrocardiographic and cineangiographic correlations in assessment of the location, nature and extent of abnormal left ventricular segmental contraction in coronary artery disease. Circulation 49:447–454, 1974
11. **Hilsenrath J, Tabrah E, Hamby RI, et al:** Relation of left ventricular contractile patterns in coronary artery disease to the electrocardiogram and vectorcardiogram. J Electrocardiol 8:335–342, 1975
12. **Kaplan MA, Harris CN, Aronow WS, et al:** Inability of the submaximal treadmill stress test to predict the location of coronary disease. Circulation 47:250–256, 1973
13. **Bartel AG, Behar VS, Peter RH, et al:** Graded exercise tests in angiographically documented coronary artery disease. Circulation 49:348–356, 1974
14. **Kasser IS, Bruce RA:** Comparative effects of aging and coronary heart disease on submaximal and maximal exercise. Circulation 39:759–774, 1969
15. **Manvi KN, Ellestad MH:** Elevated ST segments with exercise in ventricular aneurysm. J Electrocardiol 5:317–322, 1972
16. **Gorlin R, Klein MD:** Prospective correlative study of ventricular aneurysm. Am J Med 42:512–531, 1967

Is the Treadmill Exercise Test Useful for Evaluating Coronary Artery Disease in Patients With Complete Left Bundle Branch Block?

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To aid in the study of coronary artery disease, 57 patients with complete left bundle branch block underwent clinical evaluation, treadmill exercise testing and cardiac catheterization. The patients were classified into two groups according to coronary angiographic findings: 30 patients with significant stenosis (70 percent or greater luminal narrowing) of at least one major vessel and 27 with no significant coronary artery disease. There was no difference in age, presenting symptoms or previous medical treatment between the two groups. There were more men in the group with coronary artery disease. Exercise-induced S-T changes were similar in the two groups; the sensitivity and specificity of these changes for the diagnosis of coronary artery disease were unacceptable irrespective of the criterion chosen. With additional S-T depression of either 1 or 2 mm below the baseline value, the predictive accuracy was only 53 percent. Combined exertional chest pain and 1 mm S-T depression increased the predictive accuracy of exercise testing to 71 percent. These data indicate that exercise-induced electrocardiographic changes do not facilitate detection of coronary artery disease in patients with complete left bundle branch block.

Exercise-induced electrocardiographic changes are the most widely recognized noninvasive indicators of myocardial ischemia. The specificity of the exercise electrocardiogram is dependent upon the normalcy of the resting electrocardiogram.[1,2] By altering the pattern of ventricular activation and recovery, left bundle branch block produces major QRS and ST-T changes at rest and during exercise. Nonetheless, several authors[3,4] have suggested that exertional ST-T changes can provide useful information on ischemia, particularly if more precise interpretative criteria are adopted.[5,6] To assess the validity of this view we evaluated the results of stress testing, coronary angiography and left ventriculography in 57 patients with left bundle branch block.

Material and Methods

Ninety-one patients with evidence of left bundle branch block in a resting electrocardiogram underwent a multistage treadmill exercise test at this institution between July 1, 1971 and June 30, 1976. Of these patients, 57 were simultaneously evaluated with coronary angiography and left ventriculography. The treadmill exercise test was performed according to a modified Bruce protocol.[7] A complete 12 lead electrocardiogram was recorded before and serially after exercise, and 6 precordial leads were monitored and recorded every minute during exercise. All patients were encouraged to exercise to the maximum of their physical capacity. Reasons for termination of the test included increasing chest pain, exhaustion, dyspnea, leg pain, arrhythmias, conduction disturbances and attainment of the predicted maximal heart rate. S-T segment depression was measured by comparing it with the P-R segment, and the maximal deviation

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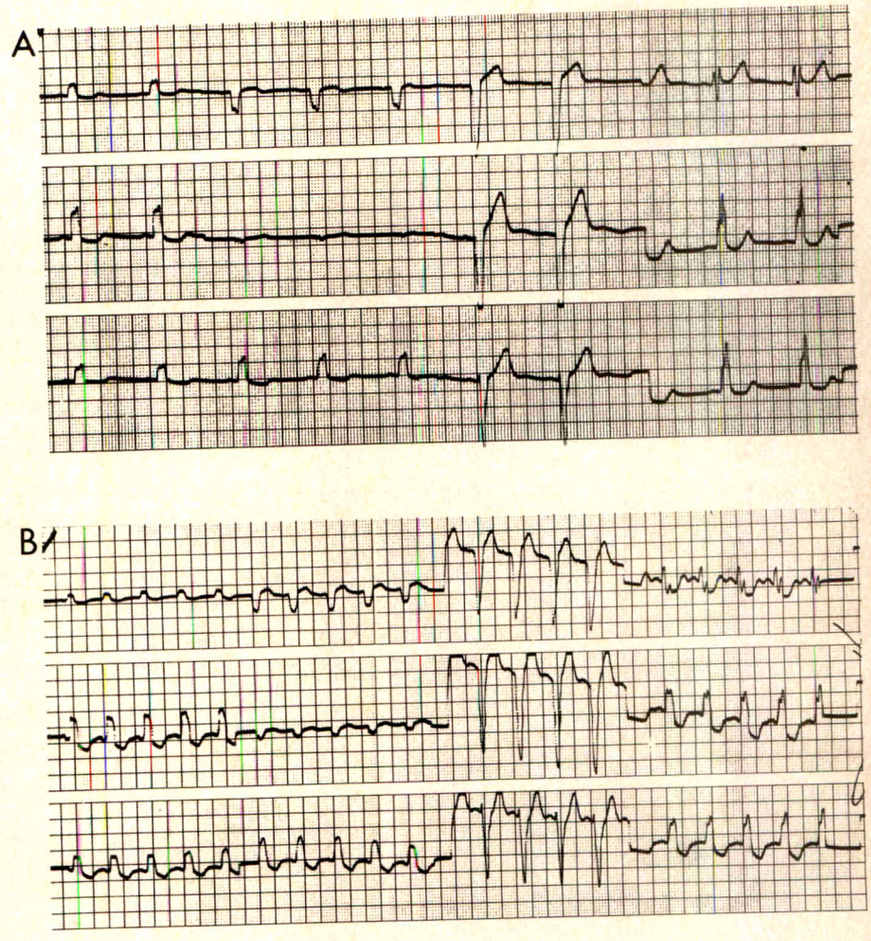

FIGURE 1. Twelve lead electrocardiograms of a patient with coronary artery disease showing complete left bundle branch block. **A,** at rest. The order of the leads is as follows: **Top row,** I, aVR, V_1, V_4; **middle row,** II, aVL, V_2, V_5 and **bottom row,** III, aVF, V_3, V_6. **B,** 15 seconds after exercise, showing additional S-T depression of more than 2 mm in leads V_4 to V_6.

in a precordial lead (generally V_4, V_5 or V_6) was used for purposes of analysis. The coronary angiograms were performed in multiple projections according to the Sones technique, and a left ventricular angiogram was performed in the right anterior oblique projection, usually at the end of the study. The patient was considered to have significant coronary artery disease if 70 percent or more narrowing of the lumen of a major coronary artery was present. Left ventricular wall motion was qualitatively assessed in terms of normalcy. Segmental or diffuse abnormality of contraction, that is, hypokinesia, akinesia or dyskinesia, was recorded.

Patient groups: The patients were classified into two groups according to results of the angiographic studies: group 1 included 30 patients with significant coronary artery disease, and group 2 consisted of 27 patients who had no coronary artery disease. Pertinent clinical information obtained for each patient included the presence of angina* or atypical chest pain, history of previous myocardial infarction, previous medical treatment (with special attention to digitalis and beta adrenergic blocking agents) and the presence of other relevant cardiovascular conditions such as systemic hypertension or valvular heart disease.

* Angina was considered typical if a mid chest, retrosternal discomfort or oppressive sensation with or without radiation to the neck or arms was brought on by exertion and relieved within 2 to 5 minutes with rest.

In group 1 (significant coronary artery disease), 9 patients had single and 8 had double vessel disease; 11 had triple vessel disease, including 2 patients with significant obstruction of the main trunk of the left coronary artery. Left ventricular wall motion was normal in 6 patients; 17 patients had isolated segmental abnormality and 7 had diffuse abnormality with or without segmental abnormality. Left ventricular end-diastolic pressure was greater than 13 mm Hg in 12 patients.

In group 2 (no significant coronary artery disease), 9 patients were considered normal on the basis of overall hemodynamic and angiographic results; 12 had a possible cardiomyopathy, as judged from either mild segmental hypokinesia or mildly elevated left ventricular end-diastolic pressure of 13 to 16 mm Hg; 6 had a definite myopathy, as judged from diffuse hypokinesia, segmental hypokinesia plus mildly elevated left ventricular end-diastolic pressure greater than 16 mm Hg.

There was no age difference between the two groups. Sex distribution in group 2 was equal, but men predominated in group 1 (24 of 30). Sixteen patients in group 1 described a clinical event that was diagnosed as myocardial infarction; none in group 2 had such an event (in two patients the clinical information was questionable). True angina was diagnosed twice as frequently in group 1 as in group 2 (66 versus 37 percent), but in group 2 atypical chest pain was the presenting complaint in 11 patients (40 percent). None of the 57 patients had a serum potassium level of less than 3.8 mEq/liter.

Results*

Two mm S-T depression: With additional S-T segment depression of 2 mm below the resting level (Fig. 1) adopted as the criterion for ischemia, 7 patients with coronary artery disease (group 1) had a positive exercise electrocardiogram; in 23 the electrocardiogram remained unchanged ("false negative" response). Among these 23, only 11 achieved a heart rate of 75 percent or greater of the maximal predicted value (in 6, the heart rate was more than 85 percent of the predicted maximum). Of the remaining 12 patients, the test was discontinued in 8 because of chest pain (without accompanying ischemic changes in the electrocardiogram), in 2 because of exhaustion, in 1 because of arrhythmia and in 1 because of transient complete atrioventricular block. Only 2 of these 12 patients were taking propranolol, which could have kept them from reaching a faster heart rate.

Among the 27 patients in group 2 (no coronary artery disease), the electrocardiograms exhibited ST-T changes indicative of ischemia (false positive response, Fig. 2) in 6 and remained negative in 21. Of the six patients with a false positive response, five attained 75 percent or greater of the predicted maximal heart rate (four achieved 85 percent or greater); in the sixth patient, who was being treated with propranolol, the test was stopped because of chest pain. Only one of these six patients was taking digitalis.

1 mm S-T depression: When S-T depression of an additional 1 mm below the baseline value was used as the criterion for ischemia, 23 patients with coronary artery disease (group 1) had a positive response, but 7 had a negative test (false negative response). Of the seven, only two achieved a heart rate of 75 percent or more of the predicted maximal value and had no pain; in three of the remaining five, the test was stopped because of exertional chest pain. None of the seven was taking propranolol. When the same criterion was used in group 2, a total of 20 patients had a positive response (false positive). All 20 patients with a false positive result had a heart rate of more than 75 percent of the maximal predicted rate, and 14 attained a heart rate of 85 percent or more of the maximal predicted rate. Of the 20 patients, 3 were taking digitalis.

S-T elevation: In group 1, exertional S-T segment elevation was recorded in only one patient who had

* A table listing the detailed clinical, electrocardiographic and angiographic data on individual patients is available on request from the authors.

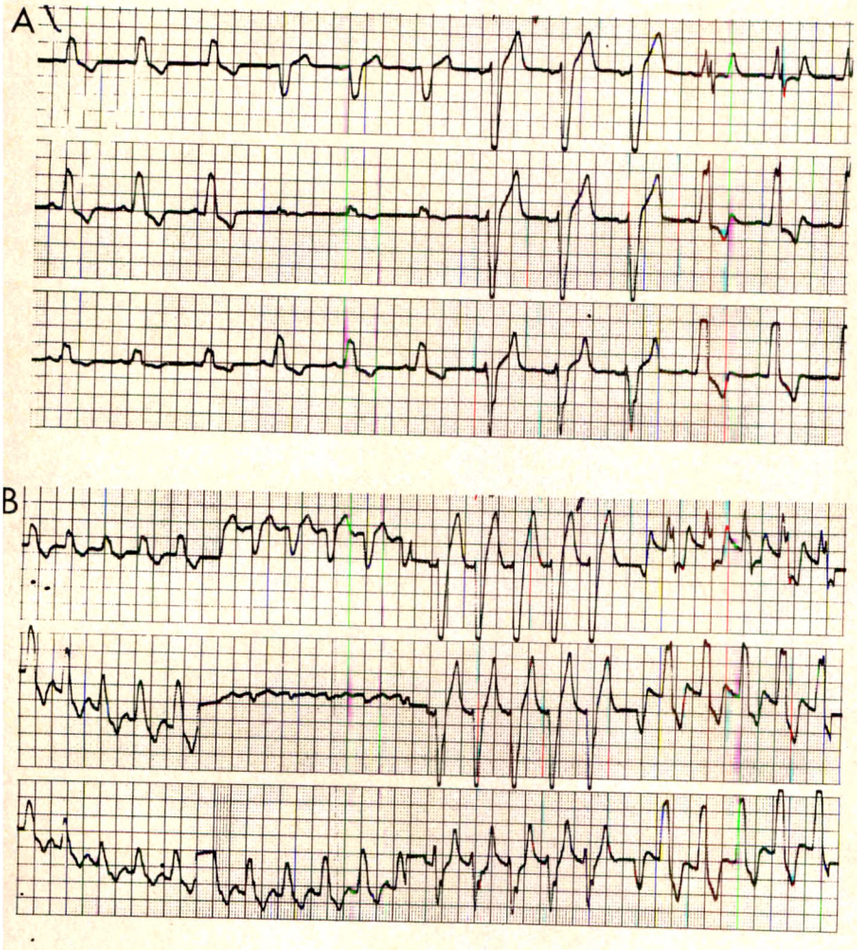

FIGURE 2. Twelve lead electrocardiograms of a patient without coronary artery disease showing complete left bundle branch block. **A,** at rest. **B,** 18 seconds after exercise, showing additional S-T depression of more than 2 mm in leads V_4 to V_6 (false positive test).

significant stenosis of the main trunk of the left coronary artery. In four other patients, the resting S-T segment was depressed at rest; on exercise it became isoelectric. No S-T elevation, whether absolute or above the resting S-T segment level, was noted among patients in group 2.

Chest pain: Thirteen patients in group 1 had chest pain during the treadmill test; only two of these, including one who was taking digitalis, manifested S-T depression of more than 2 mm below the resting level. Four of the 13 reached a heart rate 75 percent or greater of the predicted maximum (3 achieved 85 percent or greater). Of the 11 patients whose electrocardiogram remained unchanged although they experienced exertional chest pain, 5 had triple vessel coronary artery disease, 3 had two vessel disease and the remaining 3 had single vessel disease. In seven patients in group 2, treadmill exercise was interrupted because of chest pain, but only one of the seven had S-T changes indicative of ischemia.

Chest pain and 1 mm S-T depression: The combination of exertional chest pain and additional 1 mm depression of the S-T segment as an indication of ischemia was also investigated. Of the 30 patients with coronary artery disease (group 1), only 10 had a positive response based on the combined criteria; 4 patients in group 2 had a false positive response.

The method of calculation and the sensitivity, specificity, predictive value and accuracy of the various criteria for the detection of coronary artery disease are listed in Table I.

TABLE I

Results (in percent) of Calculated Sensitivity, Specificity, Predictive Value and Accuracy in All 57 Patients*

	Sensitivity	Specificity	Predictive Value	Accuracy
2 mm additional S-T depression	23	78	54	49
1 mm additional S-T depression	77	26	53	53
Chest pain	43	74	65	58
Chest pain + 1 mm S-T depression	33	85	71	58
S-T elevation (absolute or relative to resting level)	17	100	100	57

*The formulas used to calculate statistical definitions are as follows:

$$\text{Sensitivity} = \frac{\text{True Positive}}{\text{All Subjects With Coronary Artery Disease (True Positive + False Negative)}} \times 100.$$

$$\text{Specificity} = \frac{\text{True Negative}}{\text{False Positive + True Negative}} \times 100.$$

$$\text{Predictive value} = \frac{\text{True Positive}}{\text{True Positive + False Positive}} \times 100.$$

$$\text{Accuracy} = \frac{\text{True Positive + True Negative}}{\text{All Subjects}} \times 100.$$

Discussion

The clinical significance of left bundle branch block is not always clear. The etiology of this condition varies, and prognosis appears to correlate best with the presence, type and extent of the underlying cardiac disease.[8] Because ischemic heart disease is a frequent cause of left bundle branch block, and angina (the diagnostic symptom) often presents in an atypical form in patients with coronary artery disease, normal subjects or patients with unrelated cardiac conditions, a simple and safe screening test is highly desirable.

The noninvasive technique most widely used to diagnose ischemic heart disease necessitates interpretation of exercise-induced S-T changes demonstrated in the electrocardiogram. Repolarization is already abnormal in patients with left bundle branch block, and the exercise electrocardiogram generally is difficult to interpret.[9,10] However, a few reports,[5,6] based on small groups of patients, suggest that adoption of more demanding interpretative criteria (1.5 or 2 mm S-T depression) can provide reliable results. Cooksey et al.[6] believed that "the exercise electrocardiogram provides useful diagnostic information in patients with left bundle branch block"; unfortunately, only 5 of their 10 patients underwent coronary angiographic evaluation.

Exercise-induced S-T depression and left bundle branch block: In our study, the degree of S-T depression induced by exercise was not useful in detecting myocardial ischemia in patients with left bundle branch block. Our results are in agreement with the observations of Whinnery et al.,[11] who evaluated 31 asymptomatic air crewmen with left bundle branch block. Whether the criterion of an additional 2 mm S-T depression or 1 mm S-T depression is adopted, the overall accuracy of the exercise electrocardiogram remains unacceptable and does not appear to be dependent on the total number of vessels involved or the involvement of a particular vessel. A closer analysis of our patients who experienced exertional chest pain revealed that the symptom was rarely accompanied by positive S-T changes. This finding reemphasizes that such repolarization abnormalities are not necessarily an expression of ischemia and, conversely, that ischemia often fails to produce the expected electrocardiographic changes in the presence of left bundle branch block. Among the 26 patients in group 1 (significant coronary artery disease on angiography) who initially presented with chest pain, 13 (50 percent) had chest pain during the treadmill test without diagnostic S-T alterations, although 10 of the 13 had two vessel or three vessel disease. Among the 21 patients with no coronary artery disease (group 2) who were evaluated because of chest pain, 7 (33 percent) experienced chest pain during the test. These findings again indicate that either S-T segment change alone or exertional chest pain alone is unpredictable and unreliable for detecting ischemia when left bundle branch block is present. In both groups, S-T depression was seen more often in the patients who achieved the faster heart rates on exercise. However, the lower level of exercise and heart rate achieved by patients in group 1 demonstrates that the occurrence of exertional chest

pain limits the exertional capacity of patients with coronary artery disease. Elevation of the S-T segment during exercise, relative to the resting level, was encountered only in patients in group 1. This criterion therefore appears to be specific to coronary artery disease, but its sensitivity is too low to be clinically acceptable.

Repolarization abnormalities in left bundle branch block and ischemia: Feil and Brofman[3] proposed that in patients with left bundle branch block the electrocardiogram reflects the summation of the dextro- and levocardiogram, and that ischemia, primarily by causing alteration indicated in the levocardiogram, may produce S-T changes recognizable even in the presence of left bundle branch block.[3] Recent experimental work[12] revealed that in left bundle branck block not only is the left ventricle activated late, but also the spread of left ventricular wall depolarization changes from centrifugal (that is, endocardium to epicardium) to tangential. Spach and Barr[13] studied the repolarization process in an artificially provoked right ventricular ectopic beat, a condition that closely reproduces the depolarization sequence of left bundle branch block. Their results indicate that the potential distribution of repolarization was influenced by gradients that occurred from one side of the heart to the other, rather than by a gradient across the wall (that is, endocardium to epicardium) as in regular beats. If this is also true in left bundle branch block, subepicardial and subendocardial ischemia may not produce the expected ST-T changes. Moreover, Abildskov[14] demonstrated that the sequence of excitation influences the recovery phase of the electrocardiogram through two different mechanisms: It changes the sequence of repolarization, and it affects local recovery properties of the myocardium, probably by way of electronic interaction. It is possible that because of these altered recovery properties in the presence of left bundle branch block, the response to tachycardia is not the "normal" absence of S-T depression, and superimposed ischemia may not produce the expected repolarization changes of S-T depression.

Implications: Until the interplay of these and possibly other factors is better understood, exercise-induced S-T changes in patients with left bundle branch block will remain uninterpretable. Utilization of radionuclide scanning techniques with thallium and similar agents during rest and exercise may in the future prove helpful in diagnosing myocardial ischemia in the presence of left bundle branch block.

References

1. **Roitman D, Jones WB, Sheffield LT:** Comparison of submaximal exercise ECG test with coronary cineangiogram. Ann Intern Med 72:641–647, 1970
2. **Linhart JW, Turnoff HB:** Maximum treadmill exercise test in patients with abnormal control electrocardiograms. Circulation 49:667–672, 1974
3. **Feil H, Brofman BL:** The effect of exercise on the electrocardiogram of bundle branch block. Am Heart J 45:665–675, 1953
4. **Master AM, Rosenfeld I:** Exercise electrocardiography as an estimation of cardiac function. Dis Chest 51:347–383, 1967
5. **Lewis CM, Dagenais GR, Friesinger GC, et al:** Coronary arteriographic appearances in patients with left bundle branch block. Circulation 41:299–307, 1970
6. **Cooksey JD, Parker BM, Bahl OP:** The diagnostic contribution of exercise testing in left bundle branch block. Am Heart J 88: 482–486, 1974
7. **Bruce RA, Blackman JR, Jones JW:** Exercise testing in adult normal subjects and cardiac patients. Pediatrics 32:Suppl 4: 742–745, 1963
8. **Rotman M, Triebwasser JH:** A clinical and follow-up study of right and left bundle branch block. Circulation 51:477–484, 1975
9. **Riley CP, Oberman A, Lampton TD, et al:** Submaximal exercise testing in a random sample of an elderly population. Circulation 42:43–52, 1970
10. **Kattus AA:** Exercise electrocardiography: recognition of the ischemic response, false positive and negative patterns. Am J Cardiol 33:721–731, 1974
11. **Whinnery JE, Froelicher VF Jr, Stewart AJ, et al:** The electrocardiographic response to maximal treadmill exercise of asymptomatic men with left bundle branch block (abstr). Circulation 54:Suppl II:II-205, 1976
12. **Walston All, Boineau JP, Spach MS, et al:** Relationship between ventricular depolarization and QRS in right and left bundle branch block. J Electrocardiol 1:155–160, 1968
13. **Spach MS, Barr RC:** Analysis of ventricular activation and repolarization from intramural and epicardial potential distributions for ectopic beats in the intact dog. Circ Res 37:830–843, 1975
14. **Abildskov JA:** Effects of activation sequence on the local recovery of ventricular excitability in the dog. Circ Res 38:240–243, 1976

Coronary Artery Disease in Young Women: Clinical and Angiographic Features and Correlation With Risk Factors

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Coronary arteriography was performed because of suspected coronary disease in 239 women less than 45 years of age. Normal coronary arteries were found in 112 women, and a further 23 had insignificant stenosis (less than 50 percent narrowing of luminal diameter). Of the remaining 104 women, 56 had one vessel, 22 two vessel and 26 three vessel disease. Hyperlipidemia, hypertension, diabetes, smoking and a family history of coronary disease were significantly more frequent in women with significant stenosis than in women with normal arteries. Significant coronary disease was found in 55 percent (100 of 182) of women with more than two risk factors but in only 7 percent (4 of 57) of those with less than two risk factors ($P < 0.0001$). Evaluation of symptoms and the resting electrocardiogram also discriminated between women with and without coronary disease, but exercise testing was of little value. Only 4 of the 46 women with previous myocardial infarction had normal or near-normal coronary arteries. Among women with segmental wall motion abnormalities on ventriculography, the site was anterior in 90 percent (19 of 21) of women who used oral contraceptive drugs but in only 60 percent (21 of 35) of nonusers ($P < 0.05$). However, in most respects, coronary artery disease in young women does not appear to differ from coronary disease in other patients.

Several lines of evidence suggest that the characteristics of coronary artery disease in young women may differ from those in other patients. Older surveys[1–3] of hospitalized patients highlighted the rarity of symptomatic coronary artery disease in young women. The hormonal balance of premenopausal women is considered to offer partial protection against the development of coronary atherosclerosis. This concept is supported by autopsy studies[4] demonstrating more advanced coronary atherosclerosis in women with previous oophorectomy than in control women.

On the other hand, angiographically normal coronary arteries have been reported, usually in young women, in association with angina, ischemic electrocardiographic abnormalities and myocardial lactate production.[5–8] Myocardial infarction has been carefully documented in young patients who subsequently had normal coronary arteriograms but manifested ventriculographic contraction abnormalities corresponding to the electrocardiographic site of infarction.[9–12] Of the several suggested explanations of this phenomenon,[13] thrombosis in situ seems the most plausible.

After the introduction of oral contraceptive agents, many reports[14–19] suggested a relation between these agents and myocardial infarction. Recent controlled studies demonstrated that use of these agents was significantly greater among both survivors[20] and nonsurvivors[21] of myocardial infarction than among women without infarction. Coronary arteriograms in these women may be normal[22–24] but usually reveal isolated complete occlusion of the proximal left anterior descending

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coronary artery.[25] Because oral contraceptive drugs can increase coagulability,[26] these women have often been thought to have thrombotic coronary obstruction.

Because these data suggest that the etiology and pathogenesis of coronary artery disease in young women may differ from those in other patient groups, we examined the clinical and angiographic features of women less than 45 years of age who recently underwent coronary and left ventricular angiography at our institution for suspected coronary artery disease.

Young women with chest pain represent a frequent diagnostic problem in clinical practice, and the small proportion of these patients eventually requiring diagnostic coronary arteriography may account for an important part of the work load of some catheterization laboratories. If noninvasive procedures could accurately predict which of these patients were likely to have normal coronary arteries, an invasive study might become unnecessary for many. Therefore, a secondary purpose of this study was to determine which factors were predictive of normal coronary arteries in this population of young women referred for coronary arteriography.

Material and Methods

Patients: Between 1972 and 1976, a total of 7,966 cardiac catheterizations were performed at our institution. Two hundred thirty-nine women (3.0 percent of the patients undergoing this procedure) met the following criteria and constitute the study population: (1) They were less than 45 years old at the time of angiography, (2) they were studied to determine the presence or severity of coronary arterial obstructive disease, (3) they had no coexistent valvular, congenital or other type of heart disease, and (4) their coronary and left ventricular angiograms were complete and adequate for definitive interpretation.

Risk factor analysis: On admission to the hospital for coronary arteriography, each patient underwent a careful investigation of risk factors. She was questioned concerning family history of coronary artery disease and the use of cigarettes and oral contraceptive drugs in relation to the onset of symptoms. Diabetes mellitus was considered present if she was already being treated for this condition or if the fasting blood sugar level, measured in all patients during hospitalization, exceeded 140 mg/100 ml. Similarly, hypertension was diagnosed if the patient was already receiving antihypertensive drugs or if the blood pressure on admission was greater than 145/90 mm Hg. Serum cholesterol and triglyceride levels were measured in all patients after a 12 hour fast; if either was elevated, hyperlipidemia was diagnosed. Height and body weight were measured in all patients just before cardiac catheterization, and obesity was considered present if body weight for height and age exceeded the normal limits for women according to the Metropolitan Life Insurance Company tables.[27]

The presence or absence of each risk factor could not be definitely determined in all patients. Twelve women had inadequate knowledge of their family history regarding coronary disease, and data regarding cigarette usage were omitted from the records of 21 patients. In 14 normal women and 11 with significant coronary disease, the relation between the onset of symptoms and oral contraceptive usage could not be clarified, usually because the symptoms were ill defined or of long duration. In four women the diagnosis of diabetes could neither be documented nor eliminated with certainty; similarly, the possibility of hypertension could not be clarified in three. The presence or absence of hyperlipidemia could not be ascertained in 30 normal women and 10 with significant coronary disease, in some because they had normal serum lipid levels while receiving lipid-lowering drugs or diet.

Although the postmenopausal state is considered to predispose to coronary disease,[4] we were unable to evaluate this factor accurately because many of the women had previously undergone major gynecologic surgery but were uncertain if bilateral oophorectomy had been performed. The prevalence of hysterectomy, oophorectomy and ovarian cystectomy did not differ between women with coronary artery disease and those with normal arteries.

Exercise testing: On the day before cardiac catheterization the attending physician recorded whether he believed the patient's symptoms, nearly always including chest pain, were caused by coronary artery disease. All women had a resting electrocardiogram that was interpreted according to the criteria of the Minnesota code.[28,29] The final 140 of the 239 women in the study underwent exercise testing, except for 16 who were thought to have unstable angina. All exercise tests were performed in a similar fashion on a motor-driven treadmill according to a standard Bruce protocol.[30] Incapacitating dyspnea, chest pain, fatigue, important arrhythmias, development of more than 3 mm of flat S-T segment depression or attainment of maximal predicted heart rate for age were end points. In all patients the CM_5 electrocardiographic lead was monitored. Criteria for a positive exercise electrocardiogram were the development of 1 mm flat S-T segment depression or an upsloping S-T segment depressed 2 mm or more 0.08 second after the J point.

Coronary arteriography: Coronary and left ventricular angiography were performed according to previously described standard techniques.[31,32] All angiograms were interpreted by an experienced cardiovascular radiologist without knowledge of the clinical status of the patient. Coronary stenosis was considered significant if the luminal diameter of the vessel was reduced by 50 percent or more. In counting the number of arteries with significant stenosis, narrowing of marginal branches was considered to reflect disease of the left circumflex artery and stenosis in diagonal branches a reflection of left anterior descending artery disease.

Regional contraction abnormalities evident on ventriculography were described in standard qualitative terms.[33] Previous myocardial infarction was diagnosed when left ventriculography revealed a localized ventricular contraction abnormality graded as akinesia or dyskinesia. Because patients with coexistent valvular or other types of heart disease were excluded from study, these contraction abnormalities were assumed to be a result of previous myocardial infarction. Segmental wall motion abnormalities graded as hypokinesia were also considered evidence of prior myocardial infarction if the electrocardiogram met the Minnesota code criteria[28,29] for previous infarction or if the patient had had a clinically documented infarction.

Statistical methods: Data for all patients were coded and stored on a CDC-Cyber 173 computer. Statistical analyses were performed using the Statistical Package for the Social Sciences Program. A chi-square analysis was used to determine the statistical significance of differences in the prevalence rates of risk factors among groups. Patients whose risk factors were unknown were omitted from this statistical analysis because they appeared to be randomly divided among groups and constituted only a small percent of the total patient population. A multivariate analysis of risk factors and other clinical and angiographic features was performed to

TABLE I

Distribution of Angiographic Abnormalities

	Patients (no.)	Age (yr)		Distribution of Coronary Arterial Lesions (%)				SWMA		MI	
		Mean ± 1 SD	Range	LAD	LCx	RCA	LMCA	no.	%	no.	%
Normal coronary arteries	112	38.9 ± 5.0	20–40	—	—	—	—	3	3	3	3
Stenosis <50%	23	39.4 ± 4.3	31–44	61	26	57	0	2	9	1	4
1 Vessel disease	56	38.5 ± 4.6	27–44	68	11	18	4	23	41	18	32
2 Vessel disease	22	39.9 ± 3.9	31–44	82	32	77	9	14	64	10	45
3 Vessel disease	26	41.0 ± 3.2	31–44	100	92	100	18	18	69	14	54
All patients	239	39.2 ± 4.6	20–44	79	36	51	8	60	25	46	19

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LMCA = left main coronary artery; MI = myocardial infarction; RCA = right coronary artery; SD = standard deviation; SWMA = segmental wall motion abnormality.

differentiate between dependent and independent variables. Fisher's exact test was applied when appropriate. Intergroup differences of continuous variables, such as age, were tested for statistical significance using the F test.

Results

Of the 239 women qualifying for the study, 112 had normal coronary arteriograms and a further 23 women had coronary irregularities but no arterial stenosis exceeding 50 percent. Of the remaining 104 women, 56 had significant one vessel disease, 22 had two vessel disease and 26 three vessel disease; no statistically significant differences in age were found among these groups (Table I). Only two women with coronary disease and six with normal arteriograms were less than 30 years old. The mean age (±1 standard deviation) for all women was 39.2 ± 4.6 years. Among women with one vessel disease, the left anterior descending coronary artery was the most frequently involved (68 percent versus 18 percent and 11 percent for the right coronary artery and the left circumflex coronary artery, respectively (P <0.001). Segmental wall motion abnormalities occurred in 32 percent of the women with one vessel disease and 67 percent of those with multivessel disease (P <0.02).

Risk factors: Figure 1 compares the prevalence of risk factors in women with normal coronary arteries with that in women with significant coronary artery disease. Diabetes, hypertension, hyperlipidemia and cigarette smoking were much more frequent in the group with significant coronary disease than in those with normal coronary arteries (P <0.0005 for each factor). A multivariate analysis confirmed that each of these factors was an independent predictor of coronary disease in this population. A family history of excessive coronary disease was also present significantly more often in the group with coronary disease (P <0.05), but the difference was less marked than for the preceding factors. No statistically significant difference was found between these two groups in the incidence of obesity or oral contraceptive usage, although 37 percent of women with coronary disease had used oral contraceptive agents compared with 27 percent of women with normal coronary arteries. A multivariate analysis revealed no subset of patients with a combination of risk factors in which oral contraceptive usage significantly correlated with the presence of coronary disease.

Isolated hypertriglyceridemia occurred in only 30.3 percent (30 of 99) of women with hyperlipidemia; although it was more common in women with significant disease (20.4 percent) than in those with normal arteries (13.8 percent), this difference was not statistically significant.

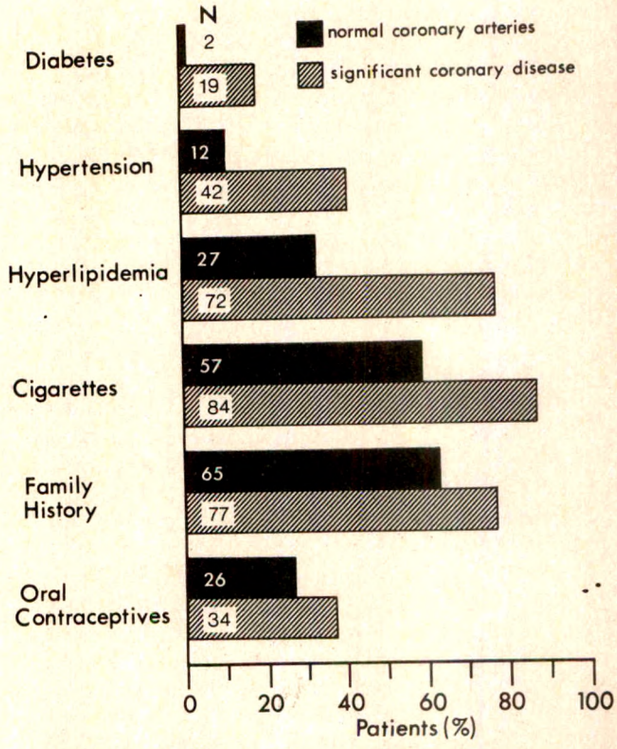

FIGURE 1. Prevalence of risk factors in women with normal coronary arteries **(black bars)** and with luminal stenosis of 50 percent or more **(hatched bars).** The differences are statistically significant for diabetes, hypertension, hyperlipidemia, cigarette smoking (P <0.0005 for all) and for a strong family history of coronary disease (P <0.05) but not for oral contraceptive agents. N = absolute number of women with risk factor.

Hyperlipidemia occurred in 64 percent of women with single vessel disease and 91 percent of those with multivessel disease ($P < 0.005$). Similarly, hypertension was found in 29 percent of women with single vessel involvement and 55 percent of those with multivessel disease ($P < 0.02$). In contrast, oral contraceptive usage was less frequent in women with three vessel disease (13 percent) than in those with one and two vessel involvement (45 percent, $P < 0.01$), and this difference was unrelated to age. Other risk factors did not vary significantly with the extent of disease.

Predictors of coronary disease: In addition to the value of these risk factors as predictors of coronary disease when taken individually, their combination correlated well with the presence of disease. Only 4 of the 57 women (7 percent) with less than two risk factors had significant coronary stenosis; 100 of the 182 (55 percent) with two or more risk factors had coronary disease ($P < 0.0001$). Thus, 100 of the 104 women (96 percent) with significant coronary disease had two or more of the risk factors evaluated.

The admitting physician's opinion as to whether the patient's symptoms, nearly always including chest pain, were typical of coronary artery disease was highly discriminatory: Symptoms were considered atypical in 63 percent of those with normal arteries but in only 16 percent of those with significant disease ($P < 0.0005$). Forty-eight percent of women with one vessel disease had atypical symptoms compared with only 7 percent of women with multivessel disease ($P < 0.001$).

A normal resting electrocardiogram was found in 52 percent of women with normal arteries but in only 28 percent of those with significant stenosis ($P < 0.001$). The final 140 women in the study underwent exercise testing on the day before coronary arteriography, except for 16 believed to have unstable angina. Eighteen of the 69 women with normal arteries or lesions of less than 50 percent had a positive test compared with 29 of the 55 women with significant coronary disease ($P < 0.005$). These high false positive (26 percent) and false negative (47 percent) rates suggest that exercise testing is of limited value in predicting the presence of significant coronary disease in this population. Multivariate analysis revealed no subgroup of patients in which exercise testing was more useful than for the overall group.

Myocardial infarction: The electrocardiograms of 45 of the 239 women revealed "definite" or "probable" myocardial infarction according to Minnesota code criteria.[28,29] On ventriculography a segmental contraction abnormality was found in 60 women. In 21 women the electrocardiogram and ventriculogram were discordant: In 18, ventriculography demonstrated a segmental contraction abnormality but the electrocardiogram did not meet the criteria for myocardial infarction; in the other 3, a normal ventriculogram was associated with electrocardiographic signs of infarction. For the purposes of this study myocardial infarction was defined solely on the basis of the ventriculogram if akinesia or dyskinesia was present (29 cases). Infarction was also diagnosed in 17 patients with hypokinesia; 13 of these met electrocardiographic criteria for infarction and the remaining 4 had a well documented clinical history of infarction.

The incidence of myocardial infarction is compared with the extent of coronary artery disease in Table I. Thirty-two percent of the 56 women with one vessel involvement and 50 percent of the 48 women with multivessel disease had evidence of previous infarction (difference not significant). Three of the 112 women with angiographically normal arteries and 1 of the 23 with less than 50 percent stenosis had ventriculographic evidence of infarction. All four of these women had previously been hospitalized with chest pain typical of myocardial infarction associated with confirmatory serum enzyme curves and evolutionary electrocardiographic abnormalities characteristic of transmural anterior infarction. Only one of these women had taken oral contraceptive agents, but all four were cigarette smokers, two were obese and three had a strong family history of coronary artery disease. All had two or more risk factors.

The mean age of the women with previous myocardial infarction did not differ from that of the entire group. Single or multivariate risk factor analysis within the group with significant coronary disease could not distinguish between women with and without previous infarction. In particular, oral contraceptive usage was not more prevalent among women with infarction than among those without.

Some differences in the prevalence of oral contraceptive usage are apparent when the site of myocardial infarction is considered. Forty-eight percent (16 of 33) of women with anterior infarction had taken oral contraceptive agents compared with only 18 percent (2 of 11) of those with inferior infarction. This difference is not statistically significant. However, 48 percent of women with anterior wall motion abnormalities (19 of 40) had used oral contraceptive agents compared with only 28 percent (44 of 155) of those with a normal left ventriculogram ($P < 0.05$) and 13 percent (2 of 16) of those with inferior wall motion abnormalities ($P < 0.05$). A multivariate analysis indicated that this difference was independent of other variables. The presence or absence of other risk factors did not correlate with either the site of infarction or wall motion abnormalities.

Discussion

This study describes the clinical and angiographic features and analyzes the risk factors of a group of women less than 45 years of age referred for coronary arteriography because of suspected coronary disease. Those who were found to have coronary disease are not necessarily representative of all young women with overt coronary disease because women with minimal or atypical signs and symptoms and those who die soon after the onset of symptoms are likely to be underrepresented. Similarly, the women in our study with normal coronary arteries cannot be considered a normal control group because all were suspected of having coronary disease.

Angiographic features: In slightly more than 50

percent of the 104 women with significant coronary stenosis (50 percent or more narrowing of luminal diameter), only one vessel was involved; 25 percent had two vessel disease and 25 percent three vessel involvement; 8 percent had 50 percent or greater stenosis of the left main coronary artery. The left anterior descending coronary artery was the site of single vessel disease in most cases.

These findings are similar to those reported by Welch et al.[34] in 236 women less than 50 years of age with coronary disease. To our knowledge no other large angiographic series of young women has been reported. The prevalence of single vessel disease in both our group (54 percent) and that of Welch et al. (43 percent) was greater than that in young men (36 percent)[35] or in unselected patients (34 percent)[36] undergoing arteriography. This difference could be age-related because younger patients have less extensive disease; however, in our study women with multivessel disease were not significantly older than those with one vessel disease.

The disproportionate involvement of the left anterior descending coronary artery in our series and that of Welch et al. has also been described in other patient populations.[35,36] However, the women in our study with insignificant coronary stenosis (less than 50 percent narrowing of luminal diameter) had equal involvement of the left anterior descending and right coronary arteries. This finding suggests that left anterior descending artery disease may predominate in patients undergoing angiography because it causes more impressive signs and symptoms, creating a bias in the selection process for angiography. We found localized ventricular contraction abnormalities in 41 percent of women with one vessel disease and in 66 percent of those with multivessel disease. This wide prevalence, particularly in single vessel disease, may also be a result of bias in the referral process for coronary arteriography.

Risk factors: Hyperlipidemia, hypertension and diabetes were at least twice as frequent in women with signifcant coronary artery disease as in those with normal arteries. Cigarette smoking and a strong family history of coronary disease also correlated significantly with coronary artery disease, but this relation was less impressive. Hypertension and hyperlipidemia were also significantly more prevalent in women with multivessel disease than in women with single vessel disease. Because the presence of multiple risk factors undoubtedly influences the decision to refer patients for coronary arteriography, women in our study with normal arteries were probably much more likely to have these factors than would an unselected group of women this age. Therefore, comparing the prevalence of risk factors in women with and without coronary artery disease as in our study, probably underemphasizes the strong correlation between risk factors and coronary disease in this population.

Previous authors[2,3,19,25] have recognized a high prevalence rate of risk factors in young women with myocardial infarction. However, risk factors have not been analyzed systematically in large groups of young women with angiographically documented coronary artery disease. Welch et al.[34] found a relation between hypercholesterolemia and the presence of coronary artery disease in women less than 50 years of age, but their study did not analyze other risk factors. In 18 of 21 young women (40 years or less) with coronary artery disease, Engel et al.[37] found at least three of the following five risk factors: hypertension, hyperlipidemia, positive family history, diabetes and smoking.

Predictors of coronary disease: Clinical features that reliably identify women with normal coronary arteries among young women with chest pain referred for coronary arteriography would be useful because normal coronary arteries are frequently encountered in this group. Risk factor analysis isolated a substantial subgroup of our study population in which coronary disease was rarely present: 57 of the 239 women in the study had less than two risk factors and only 7 percent of them had significant disease. We therefore conclude that diagnostic coronary arteriography is rarely necessary in women in this age group with less than two risk factors who are referred to our laboratory because of suspected coronary disease.

The resting electrocardiogram and the nature of the patient's chest pain were also helpful discriminators. Only 16 percent of women with significant coronary disease and only 7 percent of those with multivessel disease had atypical symptoms. Only 28 percent of those with coronary disease had a completely normal electrocardiogram. Although exercise testing may accurately predict the presence of significant coronary disease in other patient populations, the high rate of false positive (26 percent) and false negative (47 percent) tests in our study indicates that its predictive value is severely limited in these young women. Even when subsets of patients were examined, whether grouped on the basis of symptoms, the resting electrocardiogram or number of risk factors, false positive and false negative results were frequent.

The clinical features predictive of coronary disease in our study will not necessarily be equally useful when applied to women seen in other centers or in clinical practice because the composition of such groups may vary a great deal from that of our population.

Myocardial infarction and normal coronary arteries: The criteria for the diagnosis of myocardial infarction used in this study are imprecise. Because patients with valvular and other types of heart disease were specifically excluded from our series, localized akinesia or dyskinesia probably always indicated previous infarction. Similarly, previous infarction probably occurred in women with segmental hypokinesia who met strict electrocardiographic criteria for infarction or had a well documented clinical history of infarction. However, our criteria probably underestimate the true prevalence of previous infarction because patients with this finding occasionally have an entirely normal ventriculogram.[38] Thus, 3 of the 45 women in our study with myocardial infarction by electrocardiographic criteria had a normal ventriculogram. In spite of these considerations, a third of the patients with single vessel disease and half of those with multivessel disease had had a

previous myocardial infarction according to our criteria. On the other hand, only 4 of the 135 women with a normal or near-normal coronary arteriogram had had a previous infarction.

Angiographically normal coronary arteries have been reported to occur occasionally in patients with prior well documented myocardial infarction.[9–12] Most of these patients are young, and some are women taking oral contraceptive drugs.[22–24] Most, but not all, exhibit a ventricular contraction abnormality corresponding to the electrocardiographic site of infarction. The exact incidence of normal coronary arteriograms after myocardial infarction is not known, but Kahn and Haywood[11] reported this combination in 12 percent of their patients studied after infarction. Seventy-one of their 78 patients were men, and all 9 with normal arteriograms were young men. On this basis they recommended that all patients less than 50 years of age with a myocardial infarction should routinely undergo coronary arteriography to identify those with angiographically normal vessels. Only 4 of the 46 women in our study with a previous infarction had normal or near-normal coronary arteries. This small proportion suggests that in our group of young women with previous infarction, routine coronary arteriography is not indicated to detect those with angiographically normal vessels. This conclusion might change if specific effective therapy for this syndrome made a definitive diagnosis necessary.

Analysis of risk factors and other clinical findings revealed no features that distinguished women with normal arteriograms from the total group with previous infarction. Specifically, only one of the four in our series had taken oral contraceptive agents, but all four smoked cigarettes and had at least two risk factors.

Myocardial infarction and oral contraceptive agents: Recent controlled studies have demonstrated an increased use of oral contraceptive agents by both survivors[20] and nonsurvivors[21] of myocardial infarction. These agents appear to act synergistically with other risk factors. In our series the prevalence of oral contraceptive usage did not differ significantly between the group with significant coronary disease and those with normal vessels. Similarly, women with and without previous infarction, both in the total population and in the subgroup with significant stenosis, had similar rates of oral contraceptive usage. The lack of a significant correlation between these drugs and the presence of coronary disease in our study might have occurred because our patients represent a biased population or because of the difficulty in accurately establishing previous contraceptive practices in some of our patients. In any case, other risk factors such as hyperlipidemia, hypertension and diabetes seem to be more closely associated with coronary disease in this population.

Isolated obstruction of the proximal left anterior descending coronary artery is usually found on arteriography in women with infarction related to the use of oral contraceptive agents.[25] Among those with a normal arteriogram, the ventriculographic site of infarction is usually anterior.[22,24] In all young women undergoing arteriography, disease is much more frequent in the left anterior descending coronary artery than in other vessels, as observed in our study and that of Welch et al.[34]; therefore, the frequent anterior site of disease in women with infarction related to use of oral contraceptive agents should not be surprising. However, our study showed that oral contraceptive usage is significantly more frequent in women with anterior wall motion abnormalities than in other groups, independent of other variables. We cannot satisfactorily explain this finding. If hypercoagulability[39] induces thrombosis in situ and subsequent infarction in susceptible users of oral contraceptive agents, perhaps local hemodynamic factors in the proximal left anterior descending coronary artery are more likely to induce turbulence and thrombosis there than at other sites. However, we found no characteristic type of angiographic lesion in users of oral contraceptive agents; many had multiple coronary stenoses and only one had angiographically normal vessels. Further studies are needed to clarify the pathogenesis of myocardial infarction in young women taking oral contraceptive drugs.

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References

1. **Underdahl LO, Smith HL:** Coronary artery disease in women under the age of forty. Proc Staff Med Mayo Clinic 22:479–482, 1947
2. **James TN, Post HW, Smith FJ:** Myocardial infarction in women. Ann Intern Med 43:153–164, 1955
3. **Weinreb HL, German E, Rosenberg B:** A study of myocardial infarction in women. Ann Intern Med 46:285–300, 1957
4. **Wuest JH, Dry TJ, Edwards JE:** The degree of coronary atherosclerosis in bilaterally oophorectomized women. Circulation 7: 801–808, 1953
5. **Arbogast R, Bourassa MG:** Myocardial function during atrial pacing in patients with angina pectoris and normal coronary arteriograms. Am J Cardiol 32:257–263, 1973
6. **Bemiller CR, Pepine CJ, Rogers AK:** Long-term observations in patients with angina and normal coronary arteriograms. Circulation 47:36–43, 1973
7. **Waxler EB, Kimbiris D, Dreifus LS:** The fate of women with normal coronary arteriograms and chest pain resembling angina pectoris. Am J Cardiol 28:25–32, 1971
8. **Boudoulas, H, Cobb TC, Leighton RF, et al:** Myocardial lactate production in patients with angina-like chest pain and angiographically normal coronary arteries and left ventricle. Am J Cardiol 34:501–505, 1974
9. **Campeau L, Lesperance J, Bourassa MG, et al:** Myocardial infarction without obstructive disease at coronary arteriography. Can Med Assoc J 99:837–844, 1968
10. **Kimbiris D, Segal BL, Munir M, et al:** Myocardial infarction in patients with normal patent coronary arteries as visualized by cinearteriography. Am J Cardiol 29:724–728, 1972

11. **Kahn AH, Haywood LJ:** Myocardial infarction in nine patients with radiologically patent coronary arteries. N Engl J Med 291:427–431, 1974
12. **Brest AN, Wiener L, Kasparian H, et al:** Myocardial infarction without obstructive coronary artery disease. Am Heart J 88: 219–224, 1974
13. **Arnett EN, Roberts WC:** Acute myocardial infarction and angiographically normal coronary arteries: an unproven combination. Circulation 53:395–400, 1976
14. **Inman WHW, Vessey MP:** Investigation of deaths from pulmonary, coronary and cerebral thrombosis and embolism in women of child-bearing age. Br Med J 2:193–199, 1968
15. **Dear HD, Jones WB:** Myocardial infarction associated with the use of oral contraceptives. Ann Intern Med 74:236–239, 1971
16. **Waxler EB, Kimbiris D. Van den Broek H, et al:** Myocardial infarction and oral contraceptive agents. Am J Cardiol 28:96–101, 1971
17. **Maleki M, Lange RL:** Coronary thrombosis in young women on oral contraceptives: report of two cases and review of the literature. Am Heart J 85:749–754, 1973
18. **Radford DJ, Oliver MF:** Oral contraceptives and myocardial infarction. Br Med J 3:428–430, 1973
19. **Arthes FG, Masi AT:** Myocardial infarction in younger women. Associated clinical features and realtionship to the use of oral contraceptive drugs. Chest 70:574–583, 1976
20. **Mann JI, Vessey MP, Thorogood M, et al:** Myocardial infarction in young women with special reference to oral contraceptive practice. Br Med J 2:241–245, 1975
21. **Mann JI, Inman WHW:** Oral contraceptives and death from myocardial infarction. Br Med J 2:245–248, 1975
22. **Glancy DL, Marcus ML, Epstein SE:** Myocardial infarction in young women with normal coronary arteriograms. Circulation 44: 495–502, 1971
23. **Ciraullo DA:** Recurrent myocardial infarction and angina in a woman with normal coronary angiograms. Am J Cardiol 35:923–926, 1975
24. **Benacerraf A, Veron P, Morin B, et al:** Infarctus du myocarde après contraceptifs oraux. Nouv Presse Méd 6:22–26, 1977
25. **Morris DC, Hurst JW, Logue RB:** Myocardial infarction in young women. Am J Cardiol 38:299–304, 1976
26. **Wessler S, Gitel S:** Estrogen-containing oral contraceptive agents: a basis for their thrombogenicity. JAMA 236:2179–2182, 1976
27. Metropolitan Life Insurance Company: New weight standards for men and women. Statistical Bull 40:1, 1959
28. **Blackburn H, Keys A, Simonson E, et al:** The electrocardiogram in population studies. A classification system. Circulation 21: 1160–1175, 1960
29. **Rose GA, Blackburn H:** Cardiovascular Survey Methods. WHD Monograph 56, Geneva, 1968
30. **Bruce RA:** Exercise testing of patients with coronary heart disease. Ann Clin Res 3:323–332, 1971
31. **Bourassa MG, Lespérance J, Campeau L:** Selective coronary angiography using percutaneous femoral technique. Can Med Assoc J 102:170–173, 1970
32. **Lespérance J, Saltiel J, Petitclerc R, et al:** Angulated views in sagittal plane for improved accuracy of cinecoronary angiography. Am J Roentgenol Rad Ther Nucl Med 121:565–574, 1974
33. **Herman MV, Heinle RA, Klein RA, et al:** Localized disorders in myocardial contraction. N Engl J Med 277:222–232, 1967
34. **Welch CC, Proudfit WL, Sheldon WC:** Coronary arteriographic findings in 1000 women under age 50. Am J Cardiol 35:211–215, 1975
35. **Welch CC, Proudfit WL, Sones FM Jr, et al:** Cinecoronary arteriography in young men. Circulation 42:647–652, 1970
36. **Proudfit WL, Shirey EK, Sones FM Jr:** Distribution of arterial lesions demonstrated by selective cinecoronary arteriography. Circulation 36:54–62, 1967
37. **Engel HJ, Page HL, Campbell WB:** Coronary artery disease in young women. JAMA 230:1531–1534, 1974
38. **Williams RA, Cohn PF, Vokonas RS, et al:** Electrocardiographic, arteriographic and ventriculographic correlations in transmural myocardial infarction. Am J Cardiol 31:595–599, 1973
39. **Latour JG, Marchandise B, Beaulac P, et al:** Hyperaggregability of platelets to thrombin in patients with documented myocardial infarction and normal coronary arteriograms (abstr). Am J Cardiol 39:328, 1977

Nonobstructive Coronary Thrombosis in Sudden Cardiac Death

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Careful histologic studies were performed on the coronary arteries, myocardium and conduction system of the hearts of six men aged 32 to 44 years who died suddenly with no history of heart disease. All six hearts demonstrated coronary atherosclerosis without evidence of complete obstruction or myocardial infarction. A nonobstructing mural coronary thrombus was found in all six hearts; in four, the thrombus was located in the left anterior descending coronary artery. Distal microthrombi were found in four hearts.

In these six men, the terminal event, often a ventricular arrhythmia, may have been related to the mural coronary thrombus. Small fragments originating from such lesions can obstruct the microcirculation producing sudden lethal arrhythmias. Nonobstructing mural coronary thrombosis may be more prevalent and more significant than previously suspected and should be considered in cases of sudden cardiac death.

Approximately one third of the hearts in cases of sudden cardiac death exhibit acute coronary thrombosis,[1,2] and about one fifth to one fourth of the thrombi are nonobstructive.[3,4] The terminal event in sudden cardiac death is commonly ventricular fibrillation.[2] The presence of nonobstructing thrombi, particularly in the absence of other acute structural lesions in the heart or coronary arteries, suggests a relation between the arrhythmia and the coronary abnormality.

The possibility that sudden cardiac death may be related to the presence of a nonobstructing thrombus, particularly to showers of microemboli,[5,6] led us to study the postmortem angiograms and perform an extensive histologic examination of the hearts of six young men with no history of heart disease whose death was sudden and unexplained.

Materials and Methods

All hearts were obtained fresh, intact and unembalmed from the Sacramento County coroner's office. The basis for selection was the sudden unexplained death of a man less than 45 years of age with no history of heart disease. The hearts, selected at random over a period of 2 years, represent six consecutive hearts submitted for this study. All six hearts had patent coronary arteries, and none had evidence of old or recent myocardial infarction. Eleven hearts were used as controls: three human hearts from men aged 19 to 46 years who died suddenly of noncoronary causes and eight pig hearts obtained fresh from a slaughterhouse.

Gross study and postmortem angiography: After the hearts were weighed and studied radiographically, each artery was injected with a barium gelatin mass of a different color (Fig. 1A). The technique of injection and the consistency and composition of the injection mass have previously been described.[7] The hearts were fixed in formalin, and the epicardial coronary arteries were dissected intact from the external surface of the heart. These dissected arteries were subjected to X-ray study, decalcified and then restudied radiographically (Fig. 1B). The full length of each artery was cut into 2 to 3 mm cross sections and embedded for histologic study.

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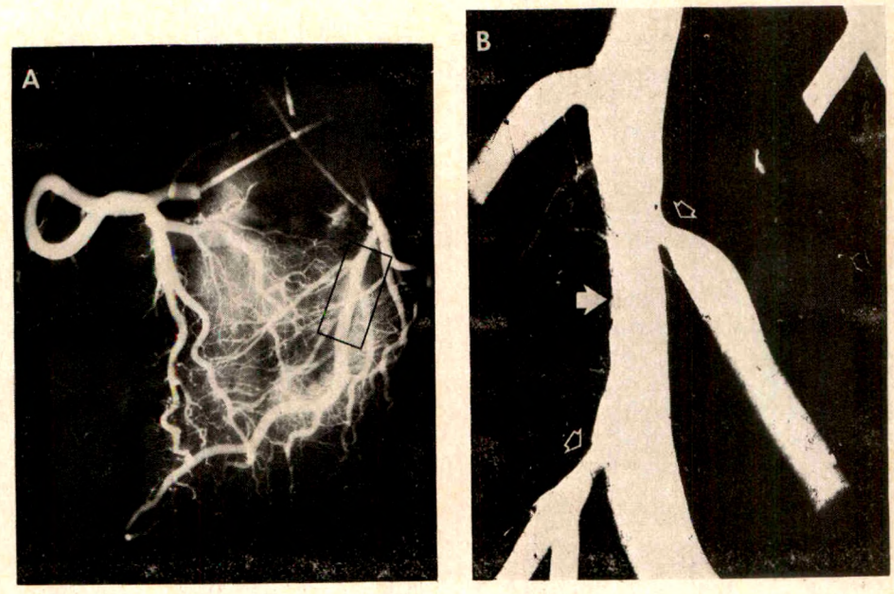

FIGURE 1. Case 1. Postmortem angiogram demonstrating patent coronary arteries. **A,** slight irregularity of the left anterior descending branch **(rectangle). B,** close-up view of the rectangular area in **A,** demonstrating mild narrowing and irregularity of the lumen **(solid white arrow).** The proximal and distal branches are also mildly narrowed at their origin **(open arrows).**

Each heart was sliced in bread loaf fashion from the apex to the base, stopping approximately 2.5 cm below the apex of the interventricular septum. Multiple myocardial sections were taken for histologic study. The sinus and atrioventricular nodes were sectioned and embedded for histologic study. X-ray films were taken before sectioning to ensure patency of the nutrient arteries to the two nodes.

Histologic preparation: A microscopic slide of each coronary section was prepared and stained with hematoxylin-eosin. Subserial sections were made whenever an attached thrombus was found (Fig. 2, A and B). These subserial sections encompassed the entire thrombus, including its proximal and distal portions. All subserial sections were stained alternately with hematoxylin-eosin and phosphotungstic acid-hematoxylin. Planimetry was performed on each coronary cross section, including the subserial sections, to determine the degree of coronary arterial narrowing. The blood supply to the A-V node, His bundle and proximal bundle branches was traced microscopically.[7]

The myocardial sections and the A-V nodal block sections were stained with hematoxylin-eosin, Masson's trichrome, phosphotungstic acid-hematoxylin and Martius scarlet blue stain. All myocardial sections were thoroughly searched for microthrombi in the myocardial arteries and arterioles to obtain evidence of antemortem thrombosis (Fig. 2C). Platelet aggregates alone, without evidence of fibrin formation, were not considered sufficient evidence of antemortem thrombosis.[8]

Results

Coronary arterial findings: The postmortem findings in these six cases are shown in Table I. Five of the six hearts were slightly hypertrophied (400 g). A nonobstructing mural coronary thrombus (Fig. 2A) was found in all cases. The left anterior descending coronary artery was the most common site of the thrombus, and the attachment was usually more than 5 mm long.

TABLE I

Postmortem Findings in Six Men With Nonobstructing Mural Coronary Thrombus

Case no.	Age (yr)	Heart Weight (g)	Nonobstructing Thrombus			
			Site	Length (mm)	Stenosis At Site (%)	Distal Micro-emboli
1	36	463	Mid LAD	12–15	58	Yes
2	44	427	Prox LAD	2	75	Yes
3	32	377	Mid LAD	8–12	96	Yes
4	37	405	Prox RCA	2–4	67	No
5	44	400	Dist LCx	8–12	68	No
6	43	437	Mid LAD	8–12	95	Yes

Dist = distal; LAD = left anterior descending artery; LCx = left circumflex coronary artery; NT = nonobstructing thrombus; Prox = proximal; RCA = right coronary artery.

Definite distal microthrombi were present in four cases. Control human and pig hearts had no evidence of nonobstructing coronary thrombi or distal microthrombi.

Assessment of the degree of narrowing elsewhere in the coronary arteries revealed that a majority of the hearts had significant two vessel disease. The thrombus was found at the site of maximal narrowing of the affected artery in one half of the cases (Table II). It was located proximal to the first septal artery in two cases and proximal to the A-V nodal artery in two cases.

Conduction system and myocardium: The microscopic blood supply to the conduction system appeared intact and followed the normal pattern in five of the six hearts.[7] No microthrombi were found in the sinus node, A-V node or His bundle. There was no evidence of disease or injury to the sinus or the A-V node. Examination of the myocardium and the peripheral Purkinjė system revealed no evidence of acute infarction in any of the selected or control hearts.

Discussion

The patients in our study who died suddenly of cardiac causes had acute thrombi in their coronary arteries that did not completely obstruct the channel. These thrombi were firmly attached to the arterial wall and were of significant size (Table I). Their surfaces were irregular with many loosely attached fragments (Fig. 2, A and B). The degree of thrombotic organization suggests that these thrombi were present some time before death, in agreement with the findings of Baba et al.[9]

All thrombi were superimposed on atherosclerotic lesions, but the thrombus was located at the site of

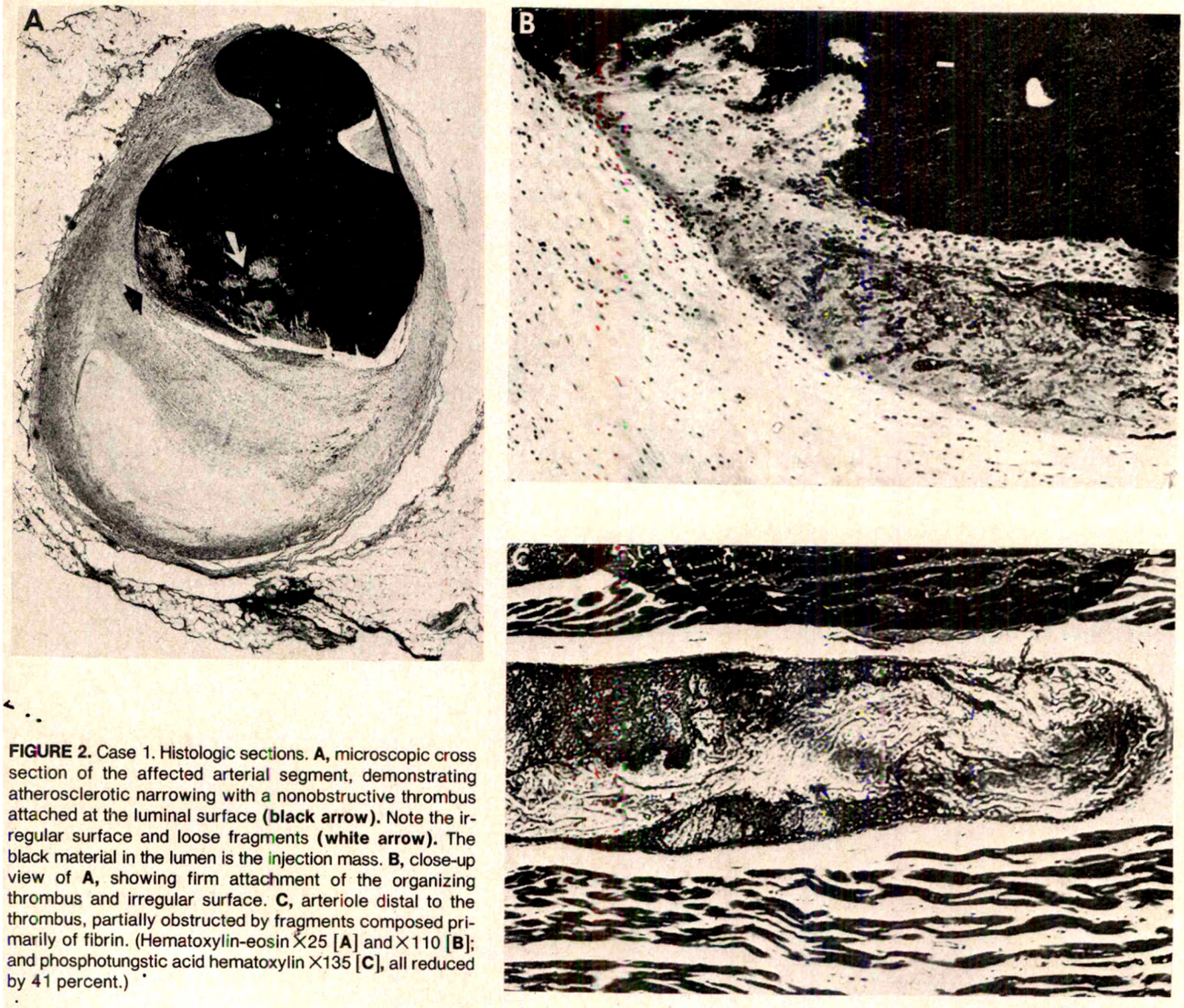

FIGURE 2. Case 1. Histologic sections. **A,** microscopic cross section of the affected arterial segment, demonstrating atherosclerotic narrowing with a nonobstructive thrombus attached at the luminal surface **(black arrow).** Note the irregular surface and loose fragments **(white arrow).** The black material in the lumen is the injection mass. **B,** close-up view of **A,** showing firm attachment of the organizing thrombus and irregular surface. **C,** arteriole distal to the thrombus, partially obstructed by fragments composed primarily of fibrin. (Hematoxylin-eosin ×25 [**A**] and ×110 [**B**]; and phosphotungstic acid hematoxylin ×135 [**C**], all reduced by 41 percent.)

greatest narrowing of the affected artery in only 50 percent of cases (Table II). Acute thrombi do not necessarily develop at the site of maximal narrowing, and the degree of narrowing is not always 75 percent or greater. The presence of both loosely attached surface fragments and distal microthrombi in the distribution of the same artery suggest that such fragments may be embolic in nature during life.

Studies in animals[10–12] and man[6,13] have shown that partial obstruction of the coronary circulation and microthrombi can produce myocardial damage and death from arrhythmia. Most thrombi at the time of inception are nonobstructive and have a potential for producing microemboli. In our cases, the consistent presence of nonobstructive thrombi and the wide prevalence of microemboli in the hearts of patients who died suddenly, as well as their absence in the control hearts and the otherwise negative postmortem findings suggest that such lesions may be an important factor in sudden cardiac death. In addition, our data establish the presence of an unrecognized acute antemortem thrombotic process in patients who died suddenly. They indicate that nonobstructive coronary thrombus can play an important role in sudden cardiac death, particularly when the clot is accompanied by emboli to the remainder of the coronary circulation.

TABLE II

Maximal Degree of Coronary Narrowing in the Major Epicardial Coronary Arteries*

Case no.	Percent Stenosis		
	LAD	LCx	RCA
1	58†	0	27
2	78†	46	78
3	96†	83	56
4	77	80	81†
5	51	75†	80
6	96†	56	68

* Assessed with planimetry.
† Artery with nonobstructing thrombus.
LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

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References

1. **Schwartz CJ, Gerrity RG:** Anatomical pathology of sudden unexpected cardiac death. Circulation 52:Suppl III:III-18–II26, 1975
2. **Liberthson RR, Nagel EL, Hirschman JC, et al:** Pathophysiologic observations in prehospital ventricular fibrillation and sudden cardiac death. Circulation 49:790–798, 1974
3. **Crawford T, Dexter D, Teare RD:** Coronary artery pathology in sudden death from myocardial ischemia. Lancet 1:181–185, 1961
4. **Roberts WC, Buja LM:** The frequency and significance of coronary arterial thrombi and other observations in fatal acute myocardial infarction. Am J Med 52:425–443, 1972
5. **Mustard JF:** Platelets and thrombosis in acute myocardial infarction. Hosp Pract 115–128, Jan 1972
6. **Haerem JW:** Sudden coronary death. The occurrence of platelet aggregates in the epicardial arteries of man. Atherosclerosis 14:417–432, 1971
7. **Frink RJ, James TN:** Normal blood supply to the human His bundle and proximal bundle branches. Circulation 47:8–18, 1973
8. **Lie JT, Titus JL:** Pathology of the myocardium and the conduction system in sudden coronary death. Circulation 52:Suppl III:III-41–III-52, 1975
9. **Baba N, Bashe WJ, Keller MC, et al:** Pathology of atherosclerotic heart disease in sudden death. I. Organizing thrombosis and acute coronary vessel lesions. Circulation 52:Suppl III:III-53–III-59, 1975
10. **Jorgensen L, Rowsell HC, Hovig T, et al:** Adenosine diphosphate-induced platelet aggregation and myocardial infarction in swine. Lab Invest 17:616–644, 1967
11. **Kordenat RF, Kedzi P:** Experimental intracoronary thrombosis and selective in situ lysis by catheter technique. Am J Cardiol 30: 640–645, 1972
12. **Moore S, Belbeck LW, Evans G:** Myocardial lesions associated with partial compared to complete thrombotic occlusion of a coronary artery (abst). Circulation 54:Suppl II:II-202, 1976
13. **Ikram H, Nicholls JC:** In situ lysis of coronary thrombosis. Am J Cardiol 32:245, 1973

Rapid Changes in Left Ventricular Dimensions and Mass in Response to Physical Conditioning and Deconditioning

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To determine the influence of training and detraining on left ventricular dimensions, echocardiographic estimates of left ventricular indexes were undertaken in two groups of young healthy subjects. The training group consisted of eight competitive swimmers who were studied serially for 9 weeks. Left ventricular end-diastolic dimension in this group increased from the pretraining value of 48.7 ± 1.7 (mean ± standard error) to 53 ± 0.2 mm by the 1st week and to 52 ± 1.7 mm by the 9th week of training ($P < 0.005$). Left ventricular posterior wall thickness increased gradually from 9.4 ± 0.4 to 10.1 ± 0.4 mm by the end of the training period ($P < 0.005$). The estimated derived indexes (left ventricular end-diastolic volume index, mass and stroke volume) also increased significantly. However, changes in ejection fraction were insignificant. Maximal oxygen uptake (VO_2 max) increased from 52 ± 3 to 60 ± 3 ml/kg per min ($P < 0.005$). The detraining group comprised six competitive runners who stopped training for 3 weeks. Left ventricular end-diastolic dimension in this group decreased progressively from the control value of 51.0 ± 3 to 46.3 ± 2.3 mm ($P < 0.005$) and posterior wall thickness from 10.7 ± 0.3 to 8.0 ± 0.7 mm ($P < 0.005$) by the end of the detraining period. Likewise, the estimated derived indexes were significantly lower in response to detraining. Detraining did not influence ejection fraction. VO_2 max decreased from 62 ± 2 to 57 ± 2 ml/kg per min ($P < 0.005$).

The results indicate that (1) exercise training-induced adaptive changes in left ventricular dimensions occur rapidly and mimic the pattern of chronic volume overload; and (2) modest degrees of exercise-induced left ventricular enlargement are reversible after cessation of training.

Cardiovascular adaptations in trained athletes include cardiomegaly, resting bradycardia and increased cardiac output in response to maximal exercise. Electrocardiographic changes include evidence of first and second degree atrioventricular block, intraventricular conduction defects and right and left ventricular hypertrophy as well as repolarization changes.[1–4] The mechanisms underlying these phenomena, described in concert as manifestations of "athlete's heart," are complex and appear to involve adaptive alterations in the myocardium, the peripheral circulation and the autonomic nervous system. Although recent studies utilizing echocardiography have confirmed the earlier observations of larger cardiac dimensions in well trained athletes than in normal sedentary persons,[5,6] little is known regarding the duration of exercise training required to induce cardiac enlargement in healthy young men or women. In addition, insufficient information is available concerning regression of exercise-induced cardiac hypertrophy after cessation of training.

A rapid and progressive decrease in the heart weight of trained rats occurs after exercise is stopped.[7] However, athletes exhibit persistent cardiac enlargement evident in chest X-ray films long after they have

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stopped training.[8,9] The purpose of this study was to determine how rapidly left ventricular enlargement develops in response to strenuous exercise and how rapidly regression of left ventricular hypertrophy follows cessation of training. In this study in which each subject served as his own control, cardiac dimensions were measured echocardiographically. Measurements of maximal oxygen consumption (VO_2 max) were utilized to evaluate the effect of training and detraining on each subject.

Material and Methods

Subjects

Training group: This group consisted of eight members of the Saint Louis University swimming team, seven men and one woman aged 17 to 19 years, who volunteered to participate in this study. No subject was engaged in any regular exercise activity for 2 to 7 months before the beginning of training. All participants had a normal history, physical examination and resting electrocardiogram. The training program was designed to prepare the swimmers for competition and consisted of 2 hour swimming sessions held 6 days a week for 9 weeks. Each subject swam a total distance of approximately 5,000 to 7,000 yards during each session. The 9 week training period was completed by all but one subject who had to interrupt training for 2 weeks because of an upper respiratory tract infection.

Detraining group: Six men, aged 18 to 22 years, who were members of the Washington University cross-country team, volunteered to stop training for a period of 3 weeks. They had all been training for at least 3 months. Each subject was running 60 to 70 miles a week at a running speed of 8 to 10 miles/hour. In general, the performance capacity of subjects in both the training and detraining groups was considered mediocre by national standards except for that of two members of the detraining group who were judged superior athletes.

Echocardiographic Measurements

Left ventricular dimensions and wall thickness were measured, and left ventricular end-diastolic volume, mass, stroke volume and ejection fraction were estimated in both groups before and serially during training or detraining. The measurements were made using an Ekoline 20A ultrasonic unit equipped with a 2.25 megahertz 10 cm focal length transducer and interfaced with a Cambridge multichannel strip chart recorder. The end-diastolic dimension was measured as the distance between the endocardial surface of the left ventricular septum and the posterior wall endocardium at the peak of the R wave of a simultaneously recorded electrocardiogram.[10] The end-systolic dimension was measured as the distance between the most inward excursion of the septum and the endocardial surface of the posterior wall.[11] The transducer was located between the second and the fourth left intercostal space and angulated to ensure simultaneous visualization of the left ventricular posterior wall and septum just below the mitral valve apparatus, that is, at the level of posterior chordae tendinae. All recordings were made with the subjects supine during held expiration, and care was taken to avoid an involuntary Valsalva maneuver.

To ensure reproducibility and to minimize the inherent technical limitations in such measurements, the exact topographic location of the transducer with respect to the intercostal space and its distance from the left sternal border as well as the subject's body position were noted during the initial examination, and the identical transducer location and body position were used for subsequent serial measurements. Despite these precautions, it is still possible that measurements were affected by unavoidable minor differences in angulation of the transducer, but the influence was considered minimal and unlikely to obscure the interpretation of results. Two measurements of left ventricular dimension and wall thickness were made 1 week apart during the control period. Because the values obtained were not significantly different, reproducibility did not appear to be a problem. Echocardiograms of good quality were obtained from all subjects.

The end-diastolic and end-systolic volumes were calculated as: $V = 7/(2.4 + d) \times d^3$, where V is volume and d is internal dimension. Using this equation, Teichholz et al.[12] found that, in the absence of segmental wall motion disorders, the calculated "corrected" volume correlated well with the angiographically determined volume over a wide range of dimensional values. In this respect, the estimated volume is independent of the assumption that the long axis of the ventricular cavity is twice as long as the equatorial axis. The stroke volume (SV) was calculated as the difference between the end-diastolic and end-systolic volumes. Ejection fraction (EF) was derived from the following equation: EF = SV/EDV, where SV = stroke volume and EDV = end-diastolic volume.

The left ventricular mass was calculated as follows:

$$LV(C + M)\ V = 4/3\pi\ (Dd/2 + WTd)^2 \times (2Dd/2 + WTd)$$

$$LVMV = LV(C + M)\ V - LVCV$$

$$LVM = LVMV \times 1.05$$

where LV(C + M) V = left ventricular cavity and muscle volume; Dd = left ventricular end-diastolic cavity dimension; WTd = end-diastolic wall thickness; LVMV = left ventricular muscle volume; LVCV = left ventricular cavity volume; LVM = left ventricular mass in grams and 1.05 = specific gravity of heart muscle.[13] Troy et al.[13] found a close correlation between the values for left ventricular mass obtained with the echocardiographic method and the conventional angiographic method. All the derived indexes were corrected for body surface area.

Measurement of Maximal Oxygen Uptake

The swimmers' maximal oxygen uptake (VO_2) was measured during exercise on a bicycle ergometer as previously described in detail.[14] During the maximal exercise test, oxygen uptake was measured continually with a Perkin-Elmer mass spectrometer, model MGA-1100, interfaced with a PDP-12 computer for data analysis.

The maximal O_2 uptake of runners was measured during exercise on a motor-driven treadmill.[15] Expired air was collected through breathing valves in Neoprene® meteorologic balloons. Gas fractions were analyzed with the mass spectrometer, and gas volumes measured with the use of an American dry gas meter. Oxygen consumption was calculated in the conventional fashion.[15]

The "leveling off" criterion was used to establish that the subjects had attained maximal oxygen uptake. This method involves increasing the work intensity until an increase in work load does not result in a further increase in oxygen uptake.[14]

Results

Response to Training

Changes in left ventricular dimension and derived indexes: The directly measured left ventricular end-diastolic internal dimension increased rapidly,

TABLE I

Echocardiographic Measurements and Maximal Oxygen Uptake in the Training Group (mean values ± standard error)

	Control Sedentary	Training Period			
		1 Week	3 Weeks	5 Weeks	9 Weeks
VO_2 max					
liters/min	3.67 ± 0.26	3.92 ± 0.28*	3.97 ± 0.19†	4.02 ± 0.21‡	4.20 ± 0.19‡
ml/kg per min	51.8 ± 2.0	55.2 ± 2.8*	57.3 ± 2.8†	58.0 ± 3.2‡	59.7 ± 2.6*
LVID (mm)	47.8 ± 1.7	53.0 ± 2.1*	52.0 ± 1.7*	51.0 ± 1.9*	52.0 ± 1.7*
PWT_D (mm)	9.4 ± 0.4	9.5 ± 0.3	9.9 ± 0.4	10.1 ± 0.5‡	10.1 ± 0.4*
LVEDV (ml/m^2)	57.4 ± 4.0	73.3 ± 6.1*	70.2 ± 4.2*	67.5 ± 5.1*	69.7 ± 4.4*
LV mass (g-m^2)	84.1 ± 5.2	103.9 ± 7.8‡	105.7 ± 6.8‡	105.2 ± 7*	108.8 ± 5.5*
SVI (ml/m^2)	36.3 ± 2.6	48.2 ± 4.3†	46.8 ± 2.2†	43.5 ± 2.9†	43.1 ± 2.9*
EF	0.63 ± 0.02	0.66 ± 0.01	0.67 ± 0.02	0.65 ± 0.02	0.62 ± 0.02
HR (beats/min)	70.1 ± 4.6	72.4 ± 3.5	64.9 ± 3.5	63.0 ± 4.2	62.6 ± 5.6

*, †, ‡ Probability (P) values <0.005(*), <0.01(†) or <0.02(‡) (control versus training period).
EF = ejection fraction; HR = heart rate; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVID = left ventricular internal dimension; LV mass = left ventricular mass; PWT_D = posterior wall thickness at end-diastole; SVI = stroke volume index; VO_2 max = maximal oxygen uptake.

attaining the highest value after 1 week of training. No further significant change in this dimension occurred during the remainder of the training period (Table I, Fig. 1). The end-diastolic volume in each subject also increased significantly in response to 1 week of endurance training and remained elevated throughout the training period (Table I).

In contrast to the changes in left ventricular dimensions that occurred early during endurance training, no significant increase in measured left ventricular posterior wall thickness was seen until the 5th week of training (Table I). Estimated left ventricular mass was significantly increased after the 1st week of training. Resting stroke volume index was highest after 1 week of training and remained elevated throughout the training period. These changes were statistically significant. In contrast to the rise in stroke volume index, ejection fraction was not significantly altered by endurance training. Heart rate was insignificantly lower when compared with values before training (Table I).

Maximal oxygen uptake (VO_2 max): This value was increased by an average of 7 percent with 1 week of training and continued to increase to 15 percent by the 9th week (Fig. 2, Table I). Values attained after the 3rd, 5th and 9th weeks of training were significantly higher than the pretraining values. The average increase in VO_2 max was parallel with the average increase in left ventricular mass (Fig. 2). No significant change in body weight occurred (71 ± 3.3 kg before training versus 71 ± 3.6 kg in the 9th week of training).

Changes After Cessation of Training

Alterations in left ventricular dimensions: Left ventricular internal dimension at end-diastole decreased progressively during the 3 week detraining period (Fig. 1). This decrease became apparent after 4 days of rest and was most marked at the end of the detraining period (3rd week) (Table II). Left ventricular volume decreased by approximately 10 percent over the 3 weeks of detraining. Left ventricular posterior wall thickness decreased significantly with detraining. Compared with the control value, estimated left ventricular mass in the

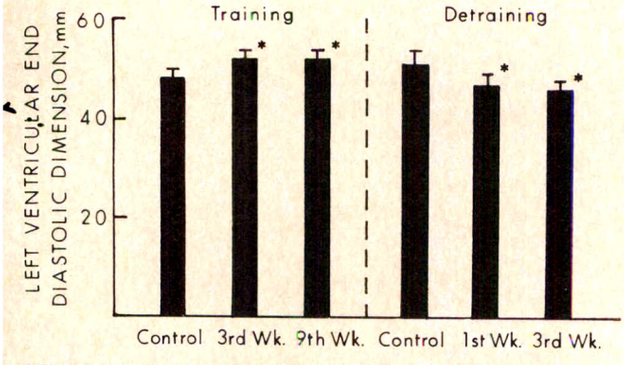

FIGURE 1. Serial changes in left ventricular end-diastolic dimensions in response to training and detraining. **Bars** and **vertical slashes** indicate mean ± standard error.* Probability (P) <0.005 (control versus training and detraining period). Wk. = week.

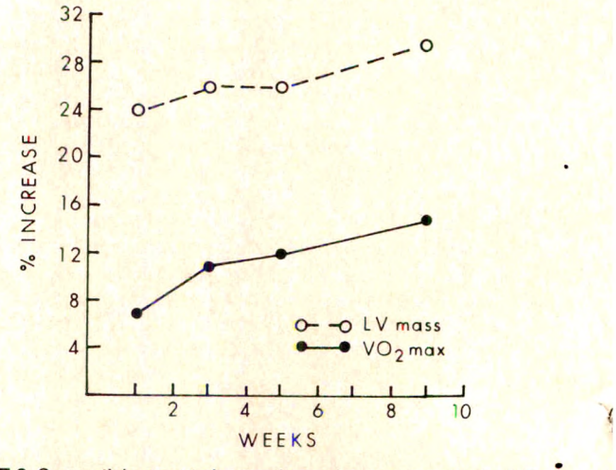

FIGURE 2. Sequential percent changes in maximal oxygen uptake (VO_2 max) and left ventricular (LV) mass during the 9 weeks of intense physical training.

TABLE II

Echocardiographic Data and Maximal Oxygen Uptake in the Detraining Group (mean values ± standard error)

	Control Running	Detraining Period				
		2nd Day	4th Day	1 Week	2 Weeks	3 Weeks
VO_2 max						
liters/min	4.27 ± 0.28	. . .	. . .	4.08 ± 0.35†	4.00 ± 0.33†	3.96 ± 0.28*
ml/kg per min	62.3 ± 2.4	. . .	. . .	56.4 ± 2.6†	57.2 ± 1.8†	56.7 ± 1.9*
LVID (mm)	51.0 ± 3.0	50.0 ± 3.1	49.4 ± 2.6†	47.0 ± 2.6*	46.8 ± 2.3*	46.3 ± 2.3*
PWT_D (mm)	10.7 ± 0.3	10.0 ± 0.3	9.6 ± 0.4†	9.0 ± 0.4†	8.2 ± 0.7*	8.0 ± 0.7*
LVEDV (ml/m^2)	64.5 ± 5.4	64.1 ± 6.6	61.9 ± 4.9‡	56.7 ± 5.2*	55.2 ± 4.4*	53.8 ± 4.4*
LV mass (g/m^2)	109.5 ± 6.4	109.6 ± 8.4	92.7 ± 5.3*	80.23 ± 5.5*	70.2 ± 8*	67.13 ± 8.1*
SVI (ml/m^2)	43.8 ± 3.9	42.1 ± 4.6	41.7 ± 2.5	40.0 ± 3.5	36.1 ± 2.9*	33.9 ± 2.6*
EF	0.68 ± 0.03	0.65 ± 0.03	0.68 ± 0.03	0.69 ± 0.02	0.66 ± 0.02	0.63 ± 0.02
HR (beats/min)	57.3 ± 6.1	54.6 ± 4.8	51.2 ± 3.2	54.2 ± 3.6	61.2 ± 6.5	63.8 ± 7.3

*, †, ‡ Probability (P) values <0.005(*), <0.01(†) or <0.02 (control versus detraining period).
EF = ejection fraction; HR = heart rate; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVID = left ventricular internal dimension; PWT_D = posterior wall thickness at end-diastole; SVI = stroke volume index; VO_2 max = maximal oxygen consumption.

test period was significantly reduced (Table II, Fig. 3). A significant decrease in stroke volume index was noticeable after 2 weeks of detraining, but ejection fraction did not change significantly. Heart rate increased progressively but insignificantly (Table II).

Maximal oxygen uptake (VO_2 max): This value decreased significantly by an average of 11 percent after 1 week of detraining and remained virtually unchanged for the next 2 weeks (Table II). The subjects' body weight increased insignificantly during the entire detraining period (69 ± 5 kg before training compared with 70 ± 5 kg in the 3rd week).

Discussion

Effects of physical training: Cardiac enlargement in athletes trained for endurance has been recognized for many years and confirmed in recent ultrasonic studies.[5,6] Inherent technical limitations in echocardiographic assessment of left ventricular dimension, volume and mass are well recognized. The potential difficulties, especially in longitudinal studies requiring serial measurements, include variations in body position, the effect of respiration, and differences in transducer location and direction of the ultrasonic beam. To minimize some of these difficulties in our study, the subject's body position and the transducer location were similar during each recording, and all echocardiographic examinations were carried out during held expiration. However, even under these strict conditions, minor variations in the direction of the ultrasonic beam are virtually unavoidable and can introduce error in the measured and derived indexes. In addition, changes in diastolic filling period can conceivably affect these measurements, although, this influence was considered unlikely because the changes in heart rate were insignificant.

The results of this study in which each subject was used as his own control indicate that the anticipated increase in left ventricular internal dimension and its derived indexes occurs very rapidly in response to vigorous physical training. Although the increased values for left ventricular internal dimension and volume exceeded the upper limit of normal range in only two subjects, these values increased in every subject in response to training. Roeske et al.[6] also noted enlarged dimensions beyond the upper limit of normal range in only 50 percent of the athletes tested. The magnitude of endurance training in our subjects was considerable, as evidenced by an average increase in maximal aerobic power of 15 percent. The increase in maximal oxygen uptake in response to endurance training is variable, and in most healthy sedentary persons ranges from 10 to 20 percent.[14]

In contrast to the rapid increase in end-diastolic dimension and volume, the changes in posterior wall thickness occurred gradually and became significant only late in the training period. Wyatt et al.[16] reported significant increases in left ventricular wall thickness and mass in dogs that were exercised regularly for 12 weeks. In dogs subjected to a chronic volume overload induced by a large arteriovenous fistula, end-diastolic volume increases initially and left ventricular wall thickness later. However, ejection fraction and mean

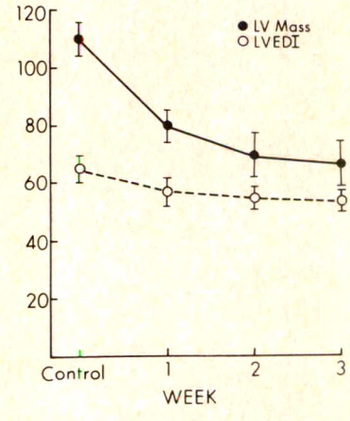

FIGURE 3. Sequential changes (mean ± standard error) in left ventricular mass (LV Mass, g/m^2) and left ventricular end-diastolic volume index (LVEDI, ml/m^2) during the detraining period.

velocity of circumferential fiber shortening remain unchanged.[17,18] The results of our study suggest that a similar response occurred in the training group.

Effects of detraining: Data on regression of exercise-induced cardiac enlargement in athletes who stop training are not clear. Several studies have shown persistence of cardiac enlargement in the conventional chest roentgenograms of former athletes.[8,9] However, rats exhibit a progressive reduction in heart weight after cessation of exercise.[7] Our findings in athletes who volunteered to detrain for a period of 3 weeks suggest that modest degrees of left ventricular enlargement are reversible. All subjects avoided any vigorous physical activity for several hours before each echocardiographic examination. Thus, significant body fluid loss with resultant reduction in heart size known to occur after prolonged heavy exercise cannot account for the persistently smaller left ventricular dimension in the detraining group.[19] Despite the reduction in end-diastolic volume, changes in ejection fraction were negligible, suggesting that mechanical performance of the left ventricle may not be affected significantly by deconditioning.

Our results indicate that adaptive changes in left ventricular dimensions and wall thickness occur quickly in response to endurance training and regress rapidly after cessation of training. However, additional studies are needed to clarify the regression of massive cardiac hypertrophy in response to detraining.

Acknowledgment

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References

1. **Gott PH, Roselle HA, Crampton RS:** The athletic heart syndrome. Arch Intern Med 122:340–344, 1968
2. **Clausen JP:** Circulatory adjustments to dynamic exercise and effect of physical training in normal subjects and in patients with coronary artery disease. Prog Cardiovasc Dis 10:459–498, 1976
3. **Lichtman J, O'Rourke RA, Klein A, et al:** Electrocardiogram of the athlete. Arch Intern Med 132:763–770, 1973
4. **Saltin B, Blomqvist G, Mitchel JH, et al:** Response to exercise after bed rest and after training. Circulation 38:Suppl VII:1–78, 1968
5. **Morganroth J, Maron BJ, Henry W, et al:** Comparative left ventricular dimensions in trained athletes. Ann Intern Med 82:521–524, 1975
6. **Roeske WR, O'Rourke RA, Klein A, et al:** Noninvasive evaluation of ventricular hypertrophy in professional athletes. Circulation 53:286–291, 1976
7. **Hickson RC, Holloszy JO:** Time course of regression of cardiac hypertrophy following cessation of endurance exercise training (abstr). Med Sci Sports 9:55, 1977
8. **Holmgren A, Standell T:** The relationship between heart volume, total hemoglobin and physical working capacity in former athletes. Acta Med Scand 163:149–160, 1959
9. **Kilbom A:** Physical training in women. J Clin Lab Invest 28:7–34, 1971
10. **Fortuin NJ, Hood WP, Sherman E, et al:** Determination of left ventricular volumes by ultrasound. Circulation 44:575–582, 1971
11. **Feigenbaum H:** Clinical application of echocardiography. Prog Cardiovasc Dis 14:531–558, 1972
12. **Teichholz LE, Kreulen TH, Herman MV, et al:** Problems in echocardiographic volume determinations. Am J Cardiol 37:7–11, 1976
13. **Troy BL, Pombo J, Rackley C:** Measurement of left ventricular wall thickness and mass by echocardiography. Circulation 45:602–611, 1972
14. **Hickson RC, Bomze HA, Holloszy JO:** Linear increase in aerobic power induced by a strenuous program of endurance exercise. J Appl Physiol 42:372–376, 1977
15. **Saltin B, Astrand PO:** Maximal oxygen uptake in athletes. J Appl Physiol 23:353–358, 1967
16. **Wyatt HL, Mitchell JH:** Influences of physical training on the hearts of dogs. Circ Res 35:883–884, 1974
17. **Ross J Jr, McCullagh WH:** The nature of enhanced performance of the dilated left ventricle during chronic volume overloading. Circ Res 30:549–556, 1972
18. **McCullagh WH, Covell JW, Ross J Jr:** Left ventricular dilatation and diastolic compliance changes during chronic volume overloading. Circulation 45:943–951, 1972
19. **Beckner GL, Winsor T:** Cardiovascular adaptions to prolonged physical effort. Circulation 9:835–846, 1954

Association of Left Dominant Coronary Arterial System With Congenital Bicuspid Aortic Valve

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Clinical angiographic studies have documented an association of left dominance of the coronary arteries with aortic stenosis and congenital bicuspid aortic valve. The postmortem arteriograms of 973 autopsy patients were reviewed for pattern of coronary dominance and the hearts examined for the nature of any aortic valve disease. There were 673 hearts (70 percent) with a right dominant pattern, 198 (20 percent) with equal dominance and 102 (10 percent) with left dominance. Of 34 hearts with congenital bicuspid aortic valve, 10 (29 percent) had left dominance, a difference significant at the 0.005 level. Of 44 hearts with calcific aortic stenosis, an acquired valve lesion, 9 (20 percent) had left dominance. Rheumatic aortic valve disease (47 cases) and aortic regurgitation (27 cases) had no apparent relation to the coronary arterial pattern. The results confirm the association of left coronary arterial dominance with congenital bicuspid aortic valve. It is suggested that a left dominant coronary system may arise as a consequence of disproportionately decreased blood flow in the left heart chambers, one cause of which is aortic valve stenosis, during early cardiogenesis.

A striking association between a left dominant coronary arterial system and isolated aortic stenosis or congenital bicuspid aortic valve in patients with and without coarctation of the aorta has been described.[1] The possible developmental implications of a relation between aortic valve malformations and coronary arterial distribution led us to examine the association in a large group of hearts studied at autopsy.

Material and Methods

Patients from the autopsy files of The Johns Hopkins Hospital were included in this study when (1) their heart had been examined after postmortem coronary arteriography and fixation in distention[2]; (2) the coronary arteriograms were adequate to assess the pattern of coronary distribution; and (3) a pathologic interpretation of any aortic valve lesions present had been made.

At autopsy, the coronary arteries are injected with a barium-gelatin-pigment mass to which formalin is added at pressures of 100 to 130 mm Hg through cannulas tied into the coronary arteries. The heart is fixed in distention with formalin at a pressure of 30 to 40 cm water. Stereoscopic radiographs are prepared of the intact heart and of the multiple transverse sections into which it is cut.

The pattern of coronary arterial dominance was determined from the postmortem arteriograms (Fig. 1) using the same criteria applied in the clinical arteriographic study.[1] Left dominance was judged present when the posterior descending coronary artery and the posterior and lateral descending branches of the left ventricle arose from the left circumflex coronary artery. Right coronary arterial dominance was judged present when those vessels arose from the right coronary artery. Equal dominance was judged present when the posterior descending branch arose from the right coronary artery but did not extend beyond the posterior interventricular groove to give off descending branches to the left

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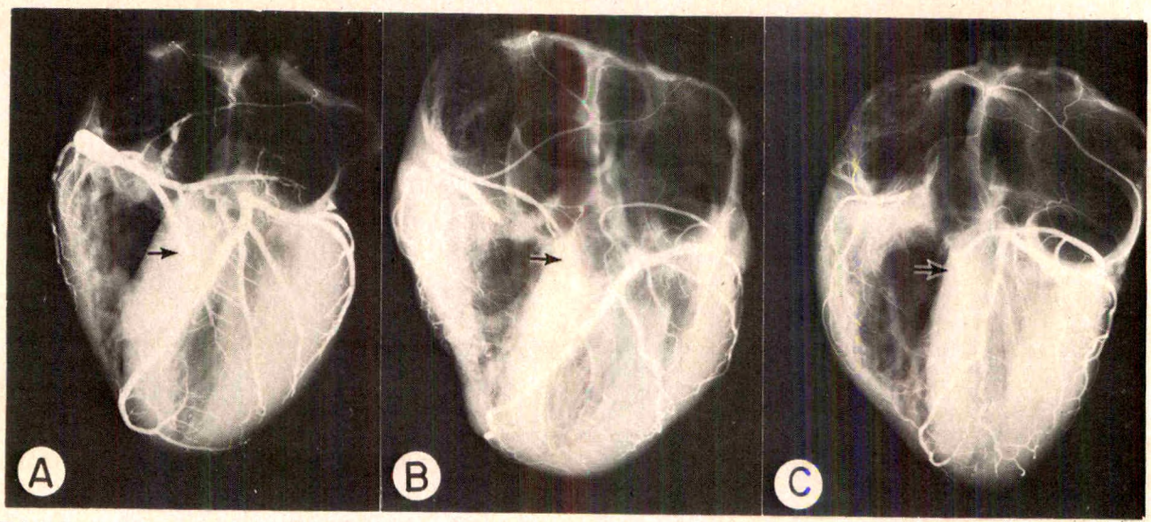

FIGURE 1. Patterns of coronary arterial distribution in postmortem arteriograms. **A,** right dominance: The posterior descending coronary artery **(arrow)** and descending branches on the inferior wall of the left ventricle arise from the right coronary artery. **B,** equal dominance: The posterior descending artery **(arrow)** but no left ventricular branches arise from the right coronary artery. **C,** left dominance: The posterior descending artery **(arrow)** arises from the left circumflex coronary artery.

ventricle. These latter vessels arose from the left circumflex coronary artery.

Identification of the nature of aortic valve disease present was based on gross examination of the heart supplemented with histologic examination when necessary. The clinical records were reviewed in each patient with aortic valve lesions for information helpful in diagnosing the lesion.

Patients were categorized according to the coronary arterial pattern and type of aortic valve lesion. Significant differences in the association of the two features in the various groups were sought using the chi-square test.

Results

The 973 patients who met the criteria for inclusion in the study are grouped according to coronary arterial pattern and type of aortic valve disease in Table I. The patients ranged in age from newborn to 95 years. In general, a patient's heart was selected for study as described if there was known or suspected cardiovascular or pulmonary disease. The series includes the majority of such patients subjected to autopsy at The Johns Hopkins Hospital since 1968. However, relatively few hearts of infants or children with congenital malformations other than aortic atresia had coronary arteriograms because of the technical difficulty of performing the injection.

Among the 973 patients, 673 (70 percent) had a pattern of right coronary arterial dominance, 198 (20 percent) had a pattern of equal dominance and 102 (10 percent) had a left dominant pattern. The only highly significant association was that between congenital bicuspid aortic valve and left coronary arterial dominance. Data on the male/female distribution in each group (Table I) reveal a significantly greater number of male subjects with left dominance in association with congenital bicuspid aortic valve and with calcific aortic stenosis.

TABLE I

Coronary Arterial Dominance, Aortic Valve Disease and Male/Female Distribution in 973 Cases

Coronary Arterial Dominance	Aortic Valve Disease (no. and percent of cases and male/female ratio)							
	None	Atresia Aortic Valve	Bicuspid Aortic Valve		Calcific Aortic Stenosis	Rheumatic Aortic Valve Disease	Regurgitant Aortic Valve	Total
			Congenital	Acquired				
Right	567 (70%); 352/215	6 (74%); 5/1	16 (47%); 15/1	8 (80%); 6/2	27 (62%); 20/7	29 (69%); 15/14	20 (74%); 14/6	673 (70%); 427/246
Equal	167 (21%); 105/62	1 (13%); 1/0	8 (24%); 5/3	1 (10%); 1/0	8 (18%); 5/3	7 (17%); 3/4	6 (22%); 5/1	198 (20%); 125/73
Left	74 (9%); 49/25	1 (13%); 1/0	10* (29%); 8†/2	1 (10%); 0/1	9 (20); 8‡/1	6 (14%); 3/3	1 (4%); 0/1	102 (10%); 71/31
Total	808 506/302	8 7/1	34 28/6	10 7/3	44 33/11	42 20/22	27 19/8	973 623/350

*, †, ‡ = probability (*P*) value <0.005 (*), <0.02 (†) or <0.05 (‡).

Discussion

Our results show that left dominance of the coronary arterial system occurs with significantly greater frequency in patients with a congenital bicuspid aortic valve. This observation confirms the finding of Higgins and Wexler[1] who, in a clinical angiographic study of adult patients with isolated aortic stenosis and children with a bicuspid aortic valve, demonstrated an unusually high frequency of a left dominant coronary arterial system.

Pathogenesis: The coronary arterial system establishes its definitive connections with the root of the aorta after the semilunar valves have formed but before they reach their definitive shape.[3] In the formation of the coronary arterial tree, an epicardial plexus is established before connections with the aorta are developed. Despite the significant statistical association between left dominance and bicuspid aortic valve, there is no absolute dependence between them because each occurs more frequently without the other. That they occur together with significant frequency suggests that some other condition predisposes to the formation of both. Coarctation of the aorta is also associated with congenital bicuspid aortic valve. Coarctation has been interpreted as the residual flow divider of the ductus arteriosus, arising when pulmonary trunk flow greatly exceeds aortic flow in early development so that ductal blood flow branches upon entering the dorsal aorta.[4] Stenosis of the aortic valve is one possible cause of the flow imbalance thought to give rise to coarctation. Another association of reduced aortic flow (with greater right heart flow) would be a small left ventricle and atrium. It is possible that disproportionate failure of enlargement of the left heart with greater expansion of the right heart chamber would permit greater growth of the coronary vascular plexus on the less rapidly expanding left side. Hence, both aortic coarctation and a left dominant coronary arterial system may be secondary to blood flow imbalance in early cardiogenesis.

References

1. **Higgins CB, Wexler L:** Reversal of dominance of the coronary arterial system in isolated aortic stenosis and bicuspid aortic valve. Circulation 52:292–296, 1975
2. **Hutchins GM, Anaya OA:** Measurements of cardiac size, chamber volumes and valve orifices at autopsy. Johns Hopkins Med J 133: 96–106, 1973
3. **Maron BJ, Hutchins GM:** The development of the semilunar valves in the human heart. Am J Pathol 74:331–344, 1974
4. **Hutchins GM:** Coarctation of the aorta explained as a branch-point of the ductus arteriosus. Am J Pathol 63:203–214, 1971

Mitral Ring Calcification in Idiopathic Hypertrophic Subaortic Stenosis

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Idiopathic hypertrophic subaortic stenosis was diagnosed in 68 patients. The diagnosis was confirmed in 24 patients with both cardiac catheterization and echocardiography, in 22 patients with catheterization alone and in 22 with echocardiography alone. Coexistent calcification of the mitral valve anulus was noted in nine patients (37 percent) studied with catheterization and echocardiography, in seven (32 percent) studied with catheterization alone and in seven (32 percent) studied with echocardiography alone. On echocardiography, mitral anular calcification was recognized as a dense thick linear echo behind the mitral valve that disappeared abruptly at the junction between the left ventricle and the left atrium. The patients with calcification of the mitral valve anulus were older (mean 64.5 years) than those without calcification (mean 47.6 years) ($P < 0.001$). Of the patients who underwent cardiac catheterization, 12 of 18 older than 55 years demonstrated mitral anular calcification as opposed to 4 of 28 younger than 55 years ($P < 0.001$). Of the patients studied with echocardiography, 7 of 14 older than 55 years demonstrated calcification compared with 0 of 8 younger than 55 years.

This prevalence of mitral anular calcification was greater ($P < 0.001$) than that found in age-matched control subjects without idiopathic hypertrophic subaortic stenosis undergoing catheterization and echocardiography. Hemodynamic data, including left ventricular pressures and outflow gradients, clinical symptoms and the prevalence of coronary disease were similar in both groups. Calcification of the mitral valve anulus is a frequent finding in older patients with idiopathic hypertrophic subaortic stenosis. Its demonstration should raise the suspicion of associated idiopathic hypertrophic subaortic stenosis.

Since the first clinical description of hypertrophic subaortic stenosis by Brock[1] in 1957, the disease has been widely recognized and studied. Both the clinical and hemodynamic findings have been extensively investigated.[2,3] The advent of echocardiography has made available a powerful tool for screening patients for abnormal systolic anterior motion of the mitral valve, asymmetric septal hypertrophy and left ventricular outflow tract observation,[3–7] and studies utilizing left ventricular angiography and echocardiography have helped to clarify the relation among these conditions. Both techniques have shown that patients may demonstrate either isolated asymmetric septal hypertrophy or asymmetric septal hypertrophy with systolic anterior motion and left ventricular outflow tract obstruction. In some instances, provocative maneuvers may evoke systolic anterior motion in patients without such motion at rest.

During the past 7 years the observation that left ventricular outflow tract obstruction, with typical findings of systolic anterior motion and asymmetric septal hypertrophy, may coexist with heavy calcification of the mitral valve anulus has been made repeatedly in this laboratory. In this report we characterize the clinical, hemodynamic and echocardiographic findings of this association.

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Methods

The results of all cardiac catheterizations performed between September 1969 and March 1977 were reviewed, and the records of 46 patients with a diagnosis of idiopathic hypertrophic subaortic stenosis were selected for further study. In each case, measurements were available of the left ventricular inflow tract pressure, obtained with a transseptal technique,[12] and left ventricular outflow pressure, obtained with retrograde left heart catheterization. Measurements of aortic and left ventricular inflow pressure were made during one or more of the following provocative maneuvers: (1) pre- and post-ventricular premature contraction; (2) Valsalva maneuver; (3) inhalation of amyl nitrite; and (4) intravenous infusion of isoproterenol.

The hemodynamic diagnosis of idiopathic hypertrophic subaortic stenosis was made in accordance with the criteria of Braunwald et al.[2] Demonstration of a pressure gradient between the left ventricular inflow and outflow tracts was accepted as evidence of this diagnosis. In 9 of the 46 patients

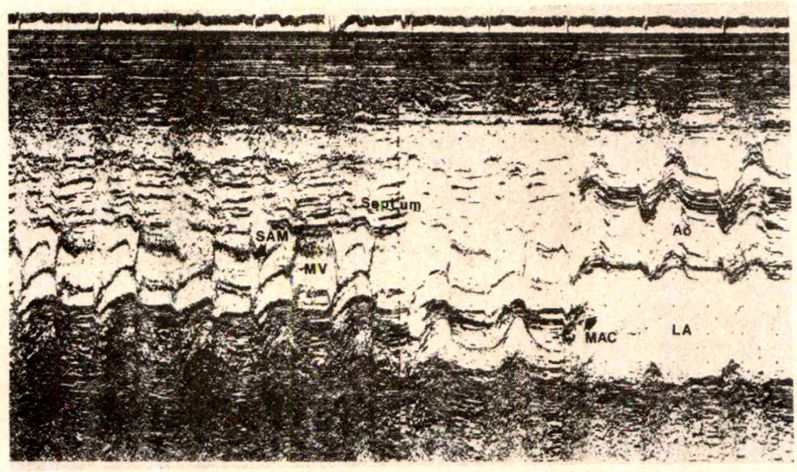

FIGURE 1. Echocardiographic scan from the left ventricle **(left)** to the left atrium (LA) **(right).** At **left,** the initial impression is that of hypertrophied posterior left ventricular wall. Only after adequate damping **(center)** is the mitral anular calcification (MAC) seen separated from the posterior wall. Ao = aorta; MV = mitral valve; SAM = systolic anterior motion of the mitral valve.

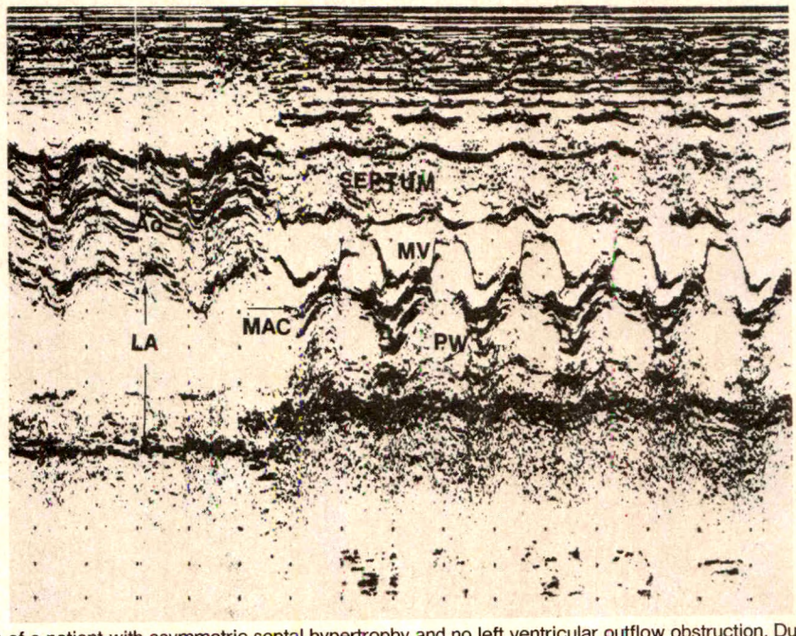

FIGURE 2. Echocardiogram of a patient with asymmetric septal hypertrophy and no left ventricular outflow obstruction. During cardiac catheterization, a gradient of 92 mm Hg was induced with isoproterenol infusion. There is mitral anular calcification (MAC) that can mimic mitral stenosis and give a false impression of small left ventricular size. PW = posterior wall; other abbreviations as in Figure 1.

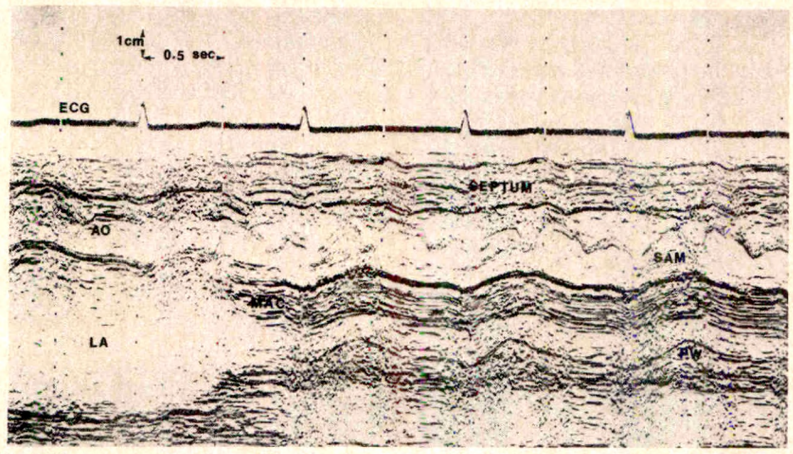

FIGURE 3. A patient with idiopathic hypertrophic subaortic stenosis and heavy mitral anular calcification (MAC). The thickness of the calcified anulus may mimic hypertrophied posterior wall and give the false impression of a symmetrically hypertrophied left ventricle. With scanning to the left atrium (LA) the echo from the anulus disappears abruptly. Abbreviations as in Figure 1.

no gradient was evident at rest, but a gradient could be induced by one of the four provocative maneuvers mentioned. In the remaining 37 patients, provocative maneuvers were used to demonstrate the presence of hypertrophic obstruction rather than fixed subvalve obstruction. Catheter entrapment was excluded by noting persistence of the gradient to a point just before the mitral valve as the catheter was withdrawn from the left ventricle to the left atrium.

Left ventricular angiography was performed in both left and right anterior oblique projections in the majority of patients. The site and extent of intracardiac calcification were evaluated fluoroscopically. Echocardiography was introduced into this laboratory in June 1972. Subsequently, 24 of the 46 patients with a diagnosis of idiopathic hypertrophic subaortic stenosis established at cardiac catheterization were also studied with echocardiography. In an additional 22 patients who did not undergo catheterization, echocardiograms were obtained that were thought to be diagnostic of this entity.

Echocardiograms were obtained using a commercially available apparatus (Ekoline 20A), and strip chart recordings (Honeywell, model 1856 strip chart recorder) of M mode displays were obtained. Asymmetric septal hypertrophy was diagnosed when the interventricular septum to posterior wall thickness ratio exceeded 1.3 and septal thickness exceeded 15 mm. Idiopathic hypertrophic subaortic stenosis was diagnosed when asymmetric septal hypertrophy coexisted with systolic anterior motion of the anterior mitral leaflet.

Mitral anular calcification was recognized echocardiographically as a thick dense linear echo behind the mitral valve. On scanning from the left ventricle to the left atrium,

TABLE I

Clinical, Angiographic and Hemodynamic Data in 16 Patients With Mitral Ring Calcification and Idiopathic Hypertrophic Subaortic Stenosis

		Hemodynamic Data						
Case no.	Age (yr) & Sex	LV Outflow Systolic Pressure (mm Hg)	LV Inflow Systolic Pressure (mm Hg)	Peak Systolic Gradient (mm Hg)	LV Diastolic Pressure (mm Hg)	Aortic Diastolic Pressure (mm Hg)	Heart Rate (beats/min)	Stroke Volume (cc/m^2)
1	68 F	100	276	176	14	66	70	32
2	62 F	152	226	74	6	92	75	27
3	63 M	126	152	36	16	67	72	38
4	72 M	118	152	44	14	69	68	39
5	65 M	148	200	52	8	66	60	53
6	71 M	120	130	10	15	70	72	40
7	64 F	151	151	0	37	74	66	56
8	70 F	176	280	104	19	68	76	37
9	49 M	148	187	39	27	66	80	43
10	72 F	114	143	39	20	60	85	49
11	53 M	110	110	0	12	68	73	38
12	49 M	130	221	91	20	85	60	45
13	64 F	137	180	53	13	90	70	58
14	65 M	116	185	69	25	70	74	42
15	73 F	104	238	134	25	52	68	28
16	61 M	150	210	60	16	70	54	57

the dense echo stops abruptly at the junction of the two chambers.[13,14]

Two other groups of patients served as controls. The first comprised of 40 randomly selected patients who underwent cardiac catheterization for cardiac disease other than idiopathic hypertrophic subaortic stenosis. The second group consisted of 40 patients who were studied in the echocardiographic laboratory for diseases other than idiopathic hypertrophic subaortic stenosis. Both groups were matched for age and sex with the corresponding patients with idiopathic hypertrophic subaortic stenosis.

The statistical significance of results was determined using the chi-square analysis or two-tailed t tests for nonpaired data.

Results

Clinical and angiographic findings: The 46 patients studied at cardiac catheterization demonstrated typical findings of idiopathic hypertrophic subaortic stenosis.[2] Sixteen of the 46 (35 percent) had fluoroscopic evidence of mitral anular calcification; their ages ranged from 51 to 78 years (mean 64.5) compared with a range of 17 to 50 years (mean 47.6) in patients without calcification (P <0.001). Mitral anular calcification was observed in 12 (66 percent) of 18 patients older than 55 years but in only 4 of 28 (14 percent) of those less than 55 years old (P <0.01). Hemodynamic, clinical and angiographic data are summarized in Table I. No significant difference was noted in any of the measured values between the groups with and without anular calcification. Similarly, there were no differences between the two groups in clinical or angiographic findings or prevalence of coronary arterial stenosis (Table II).

Anular calcification was found in only 2 of 40 patients (5 percent) who underwent cardiac catheterization for diseases other than idiopathic hypertrophic subaortic stenosis. This prevalence rate is significantly lower (P <0.001) than that in the group with idiopathic hypertrophic subaortic stenosis. Because the control patients were age-matched with the patients with idiopathic hypertrophic subaortic stenosis, there was no difference in mean age between the two groups.

Echocardiographic findings: The 24 patients who had idiopathic hypertrophic subaortic stenosis diagnosed with catheterization and echocardiography had increased septal thickness (range 15 to 22 mm, mean 19 mm), and the septal to free wall thickness ratio was greater than 1.3 in each instance. Abnormal systolic anterior motion of the anterior mitral leaflet was noted in 16 of the 24 and was induced by inhalation of amyl nitrite in an additional 2 patients. All nine patients in this group who had significant mitral anular calcification demonstrated with fluoroscopy had an additional echocardiographic finding of a thick dense linear echo behind the mitral valve. The motion of this linear echo was similar to that of the posterior left ventricular wall. When a scan from the left ventricle to the left atrium was performed, the dense echo disappeared abruptly at the atrioventricular (A-V) junction (Fig. 1 to 3).

Of the 22 patients with idiopathic hypertrophic subaortic stenosis who were studied only with echocardiography, 7 (32 percent) had a thick dense echo suggestive of mitral anular calcification. Thus, an echo suggestive of anular calcification was noted in 16 of the 46 patients (35 percent) with idiopathic hypertrophic subaortic stenosis who were studied with echocardiography (Fig. 4). Fluoroscopic confirmation was available in 9 of the 16 patients. This finding was present in 14 of 28 patients older than 55 years (50 percent) and in 2 of 18 patients younger than 55 years (11 percent). Review of the echocardiograms of 40 patients of matched age and sex, but without echocardiographic findings of asymmetric septal hypertrophy, revealed echoes suggestive of mitral anular calcification in only 2 patients (5 percent) (P <0.001) (Fig. 4).

TABLE I
(continued)

	Clinical Data						Angiographic Data	
Case no.	Angina	Asymptomatic Murmur	Atypical Chest Pains	Shortness of Breath	Syncope	ECG	Coronary Artery Disease	Mitral Regurgitation
1	+	0	0	+	0	LVH	0	Mild
2	0	0	0	+	0	AF, NSST	0	Severe
3	+	0	0	0	0	IWMI, NSST	+	0
4	+	0	0	+	0	LVH	+	0
5	0	0	0	+	+	LVH	+	0
6	0	0	0	+	0	LVH	+	Moderate
7	0	0	0	+	0	LVH	+	0
8	0	0	0	+	0	LVH	0	Moderate
9	0	0	+	+	0	LVH	0	0
10	+	0	0	+	0	LVH	0	0
11	+	0	0	0	+	LVH	0	0
12	0	+	0	0	0	LVH		0
13	+	0	0	0	0	WNL	0	0
14	0	0	0	+	0	LVH	+	Mild
15	+	0	0	+	0	LVH	+	0
16	0	0	+	+	0	WNL	0	0

AF = atrial fibrillation; ECG = electrocardiogram; IWMI = inferior wall myocardial infarction; LV = left ventricular; LVH = left ventricular hypertrophy; NSST = nonspecific S-T changes; WNL = within normal limits; + = present; 0 = absent.

TABLE II

Clinical and Angiographic Findings in 46 Patients With Idiopathic Hypertrophic Subaortic Stenosis

	Mitral Ring Calcification (16 patients)	No Mitral Ring Calcification (30 patients)
Age (yr)	51–78 (mean 64.5)	17–60 (mean 47.6)
Symptoms (no. of patients)		
Atypical chest pains	2	5
Syncope	2	4
Angina	6	11
Shortness of breath	12	13
Asymptomatic murmur	1	3
Angiographic findings (no. of patients)		
Mitral regurgitation	5	7
Coronary artery disease*	6	8
No coronary artery disease†	9	18

* Defined as obstruction of 50 percent or more obstruction of luminal diameter in one or more major branches.

† One patient with and four patients without mitral ring calcification did not undergo coronary angiography.

Discussion

Calcification of the mitral valve anulus is not an uncommon pathologic and clinical finding in patients more than 65 years old. In young patients, it is associated with metabolic abnormalities, such as Marfans syndrome and Hurler's syndrome, or defects in metabolism associated with hypercalcemia.[15,16] Although calcification of the mitral anulus is usually asymptomatic, it may cause conduction disturbances and A-V block[17] and predispose to bacterial endocarditis.[18,19] Murmurs suggestive of mitral insufficiency or aortic stenosis, or both, are audible in this condition. According to Roberts et al.[15] who studied the pathologic features of 90 patients with mitral anular calcification, mitral regurgitation is usually mild and is due to the inability of the calcium-infiltrated ring to diminish its diameter adequately during ventricular systole. An association between mitral anular calcification and conditions that cause left ventricular hypertension has been described. Ewy et al.[20] observed a greater incidence of ring calcification in hypertension and aortic valve stenosis and described a case of idiopathic hypertrophic subaortic stenosis with mitral anular calcification. Roberts et al.[15] also noted an increased frequency of such calcification in patients with accelerated atherosclerosis and diabetes mellitus. The association between idiopathic hypertrophic subaortic stenosis and mitral anular calcification was mentioned in two abstracts,[21,22] one of them from our laboratory, a few years ago.

Role of echocardiography in diagnosis: Fluoroscopy has been the procedure of choice for identifying calcification of the mitral valve anulus. Recently, echocardiography has also proved useful in detecting mitral anular calcification. Dense linear echoes just behind the mitral valve that disappear abruptly as one scans from the left ventricle to the left atrium are characteristic.[13] Because these echoes move anteriorly during systole, they may be confused with the posterior wall of the left ventricle, and thus the space behind them may erroneously be considered an echo-free space caused by pericardial effusion. In other cases, mitral anular calcification may create a false impression of mitral stenosis,[14] mask the posterior leaflet of the mitral valve or interfere with the delineation of the posterior wall of the left ventricle.

Association with hypertrophic subaortic stenosis: The role of echocardiography in the recognition of idiopathic hypertrophic subaortic stenosis has been well established, and the echographic demonstration of asymmetric septal hypertrophy and systolic anterior

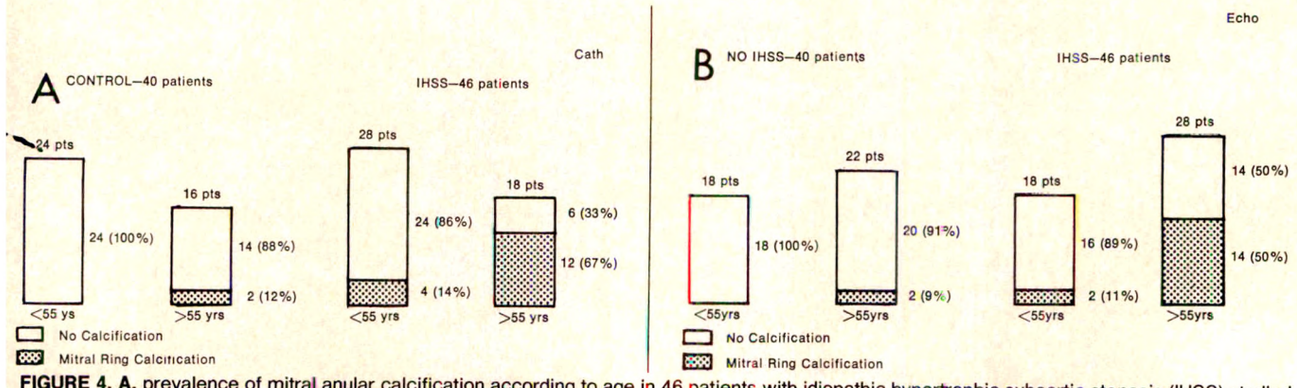

FIGURE 4. A, prevalence of mitral anular calcification according to age in 46 patients with idiopathic hypertrophic subaortic stenosis (IHSS) studied at cardiac catheterization (Cath) **(right)** and in 40 control patients **(left). B,** prevalence of mitral anular calcification according to age in 46 patients with idiopathic hypertrophic subaortic stenosis studied with echocardiography (Echo) **(right)** and 40 control patients **(left).** Twenty-four of the patients with idiopathic hypertrophic subaortic stenosis also underwent cardiac catheterization, and their data are included in panel **A.** pts = patients.

motion of the anterior mitral leaflet is considered definitive evidence of this condition. Our observations suggest that mitral anular calcification is commonly associated with asymmetric septal hypertrophy and idiopathic hypertrophic subaortic stenosis. The majority of our patients older than 55 years with idiopathic hypertrophic subaortic stenosis also had mitral anular calcification. The etiologic significance of this finding is not clear. Our results do not indicate whether anular calcification is secondary to idiopathic hypertrophic subaortic stenosis or, conversely, whether anular calcification in older patients leads to mitral valve deformity with consequent outflow tract obstruction. Prospective observation of younger patients with mitral anular calcification should provide an answer to this question. The greater prevalence of anular calcification in the group with idiopathic hypertrophic subaortic stenosis compared with the control group does indicate that this association is more than a chance finding.

Roberts et al.[15] suggested that situations that increase the pressure of mitral valve closure appear to increase lipid deposition in the mitral ring and that subsequent breakdown of these deposits is responsible for calcification. The increased prevalence of mitral anular calcification in the older patients in our series may indicate that the duration of the elevation in left ventricular pressure plays a role in this process. Although this theory may be applied to some patients in our series, we also found severe calcification in some of our patients with asymmetric septal hypertrophy who had only slight outflow tract obstruction at rest and a normal left ventricular pressure. Possibly these patients have increased left ventricular pressure at other times under the influence of exercise, increased catecholamine secretion and other factors known to influence the left ventricular outflow tract obstruction in idiopathic hypertrophic subaortic stenosis.

Clinical implications: Previously, murmurs in patients with mitral anular calcification were thought to be caused by mitral regurgitation or aortic stenosis. Our data raise the possibility that asymmetric septal hypertrophy and idiopathic hypertrophic subaortic stenosis may be a causative factor in some of these patients. Echocardiography may permit more accurate diagnosis in such cases. However, mitral anular calcification may be a source of error in interpreting echocardiograms. In addition to possibly causing an incorrect diagnosis of pericardial effusion or mitral stenosis, mitral ring calcification may result in a false negative or false positive diagnosis of asymmetric septal hypertrophy. The former situation may occur when a very thick anular echo is interpreted as the posterior left ventricular wall in patients with idiopathic hypertrophic subaortic stenosis (Fig. 1). This spurious thickening of the posterior wall would lead one away from the diagnosis of asymmetric septal hypertrophy. In addition, an erroneously low estimate of left ventricular cavity size would result from such an interpretation (Fig. 1 to 3).

If symmetric left ventricular hypertrophy is present, incorrect identification of thin mitral anular calcification as the posterior left ventricular wall will yield an erroneous diagnosis of asymmetric septal hypertrophy. Occasionally, the echoes from the anular calcium are so strong that damping to delineate them may result in loss of other important echocardiographic structures. (Fig. 3). Therefore, to avoid a host of interpretative errors, it is important to identify the abrupt discontinuation of mitral ring calcification when scanning toward the left atrium.

Acknowledgment

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References

1. **Brock R:** Functional obstruction of the left ventricle (acquired aortic subvalvular stenosis). Guys Hosp Rep 106:221–238, 1957
2. **Braunwald E, Morrow AG, Cornell WP, et al:** Idiopathic hypertrophic subaortic stenosis. Clinical, hemodynamic, and angiographic manifestations. Am J Med 29:924–925, 1960
3. **Epstein S** (moderator): Asymmetric septal hypertrophy. Ann Intern Med 81:650–680, 1974
4. **Shah PM, Gramiak R, Kramer DH:** Ultrasound localization of left ventricular outflow obstruction in hypertrophic obstructive cardiomyopathy. Circulation 40:3–11, 1969
5. **Popp RL, Harrison DC:** Ultrasound in the diagnosis and evaluation of therapy of IHSS. Circulation 40:905–914, 1969
6. **Henry WL, Clark CE, Epstein SE:** Asymmetric septal hypertrophy (ASH): echocardiographic identification of the pathognomonic anatomic abnormality of IHSS. Circulation 47:225–233, 1973
7. **Henry WL, Clark CE, Epstein SE:** Asymmetric septal hypertrophy (ASH): the unifying link in the IHSS disease spectrum. Observations regarding its pathogenesis, pathophysiology, and course. Circulation 47:827–832, 1973
8. **Fix P, Moberg A, Soderberg H, et al:** Muscular subvalvular aortic stenosis: abnormal anterior mitral leaflet possibly the primary factor. Acta Radiol 2:172–193, 1964
9. **Simon AL, Ross J Jr, Gault JH:** Angiographic anatomy of the left ventricle and mitral valve in idiopathic hypertrophic subaortic stenosis. Circulation 36:852–867, 1967
10. **Redwood DR, Scherer JL, Epstein SE:** Biventricular cineangiography in the evaluation of patients with asymmetric septal hypertrophy. Circulation 49:1116–1121, 1974
11. **Henry WL, Clark CE, Glancy DL, et al:** Echocardiographic measurement of the left ventricular outflow gradient in IHSS. N Engl J Med 288:989–993, 1973
12. **Brockenbrough EC, Braunwald E:** A new technique for left ventricular angiocardiography and transseptal left heart catheterization. Am J Cardiol 6:1062–1064, 1960
13. **Hirschfeld DS, Emlison BB:** Echocardiogram in calcified mitral annulus. Am J Cardiol 36:354–356, 1975
14. **Gabor GE, Mohr BD, Goel PC, et al:** Echocardiographic and clinical spectrum of mitral anular calcification. Am J Cardiol 38:836–842, 1976
15. **Roberts WC, Dangel JC, Bulkley BH:** Non-rheumatic valvular cardiac disease: a clinicopathologic survey of 27 different conditions causing valvular dysfunction. In, Cardiovascular Clinics, Vol 5, no 2 (Brest ANN, ed). Philadelphia, FA Davis, 1973, p 333–446

Radioautographic Studies in Experimental Myocardial Infarction: Profiles of Ischemic Blood Flow and Quantification of Infarct Size in Relation to Magnitude of Ischemic Zone

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A radioautographic method was adapted to assess regional blood flow in focal myocardial infarction produced experimentally in dogs with ligation of a branch of the left circumflex artery. Twenty-four hours later, the dogs were given an infusion of 1 millicurie of ^{14}C-antipyrine and killed. Radioautograms were prepared from 20 μ full thickness sections of the infarcted segment of each left ventricle. Adjacent tissue sections were also prepared for histopathologic study and comparison. Photodensitometric scanning of radioautograms in transverse and transmural planes permitted quantification of regional blood flow, measurement of dimensions of the zones of blood flow reduction and construction of profiles of ischemic blood flow within a cubic reference system. Thus, transverse plane scans showed symmetric profiles of decreasing blood flow from each normal margin (mean ± standard error of the mean 0.75 ± 0.11 ml/g per min) to the center of the infarct (mean 0.08 ± 0.02 ml/g per min or 11.7 ± 3.5 percent of normal flow); transmural plane scans showed an asymmetric profile of decreasing blood flow from the epicardium (mean 0.36 ± 0.06 ml/g per min) to the center of the infarct and a subsequent increase to 0.22 ± 0.03 ml/g per min near the endocardial surface.

From a comparative analysis of radioautograms with corresponding adjacent histologic sections we determined that (1) myocardial necrosis was first evident at the point of blood flow reduction that averaged 45.2 ± 3.2 percent of normal values; (2) a border zone of intermediate flow reduction where cell viability was maintained 24 hours after infarction averaged 4.5 ± 0.5 mm and encompassed 30.4 ± 3.0 percent of total ischemic zone width; and (3) on the basis of various geometric models, the size of the myocardial infarct in these experiments was approximately 40 percent of that of the ischemic zone.

In this study, we adopted the radioautographic method of Reivich et al.[1] to assess regional blood flow in experimental myocardial infarction.[2] The method provided a continuous graphic representation of the distribution of flow indicator that permitted both quantification of regional blood flow and characterization of the profiles of blood flow throughout the ischemic area. By comparing flow measurements in the ischemic zone with those of adjacent histopathologic tissue sections, we could also study the influence of blood flow on myocardial necrosis. In addition, the method permitted estimation of infarct size in relation to the magnitude of the total zone of ischemic blood flow reduction.

Methods

Experimental procedure: Studies were performed in seven mongrel dogs, weighing 20 to 28 kg, anesthetized with 30 mg/kg body weight of pentobarbital given intravenously. After endotracheal intubation, positive pressure ventilation was maintained with a Bennett model PR-1 respirator using room air supplemented with 40 percent oxygen. A left thoracotomy was performed, and the exposed heart was supported in a pericardial cradle. A single ventricular branch

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of the left circumflex artery was carefully dissected free near its origin and ligated. Previous experience from this laboratory[3] has demonstrated that this technique consistently produces a small well circumscribed myocardial infarction 1 to 2 cm in diameter. A polyethylene catheter (P.E. 160) was implanted in the left atrium through its appendage and exteriorized through the posterior thorax. After these procedures, the pericardium and left thoracotomy were closed and the animals permitted to recover.

Twenty-four hours later, each animal was lightly sedated with morphine sulfate, 15 mg intramuscularly. Under local anesthesia (Xylocaine®, 2 percent), a polyethylene catheter (P.E. 240) was inserted into the jugular vein and advanced to the right atrium, and a short polyethylene catheter was inserted in the femoral artery. Each animal was given 1 millicurie (mCi) of carbon-14–labeled antipyrine in saline solution (no. NEC-398, New England Nuclear Corporation, Boston, Massachusetts) in the form of a rapid constant rate infusion delivered directly into the left atrium over 60 seconds. Simultaneously, serial blood samples were collected from the femoral artery to obtain an arterial concentration curve of the isotope. Immediately thereafter, the circulation was arrested with a bolus injection of potassium chloride delivered directly into the right atrium. The heart was rapidly excised and the area of myocardial infarction cut transversely into 5 mm sections and immediately frozen at −25° C. Subsequently, 20 μ full thickness transmural sections of these areas were cut on a cold cryotome, placed on glass slides and rapidly dried on a warming tray at 60 °C. Macroradioautograms were prepared by placing Kodak No Screen X-Ray film plates (Eastman Kodak, Rochester, New York) directly on the tissue sections together with plastic calibration standards of known radioactivity (0.1 μCi/g; no. CFP-1, Amersham-Searle, Arlington Heights, Illinois). X-ray film plates were exposed at room temperature for 14 days and then developed using standard techniques. For comparison, adjacent transmural tissue sections were prepared with routine histopathologic methods including hematoxylin-eosin, periodic acid-Schiff and oil red O staining (see later).

Ten μliter aliquots of serum from each blood sample collected during the ^{14}C-antipyrine infusion were added to 10 ml of Aquasol (no. NEF-934, New England Nuclear Corporation), and liquid scintillation counting was performed to determine the arterial concentration of the isotope.

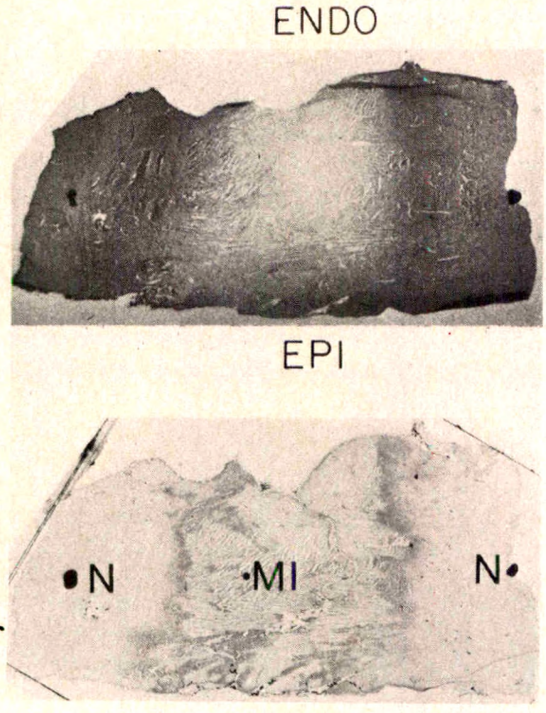

FIGURE 1. Radioautogram of a transmural section of left ventricular myocardium encompassing a region of focal ischemia **(upper panel)** and adjacent histopathologic tissue section stained with oil red O **(lower panel). Ink dots** on this figure indicate the line through which the extent of myocardial necrosis (MI_w) was estimated in the transverse plane and the direction of photodensitometric scanning through the corresponding radioautogram. A similar estimate was made in the transmural direction (MI_{td}) at 90° to the transverse plane and through the center of the infarcted zone. N = normal myocardium adjacent to ischemic zone. ENDO = endocardium; EPI = epicardium; MI = zone of myocardial infarction.

Photodensitometric scanning of the radioautograms: Scanning was performed using a Photovolt transmission densitometer and model 502 A photometer (Photovolt Corporation, New York, New York). Tissue concentrations of the isotope were determined from plastic calibration standards.* Each plastic standard had previously been exposed with 20 μ tissue sections of rat brain with a known concentration of carbon-14. Values for optical density determined with photodensitometric scanning were plotted against isotope concentration, and a best fitting curve was drawn by inspection. The standards were then assigned concentration values directly from the calibration curve. By exposing these standards for various periods of time, a series of parallel calibration curves was generated. By exposing one of the plastic standards with each film square, a calibration curve was interpolated for each radioautogram. Subsequently, the tissue concentration of isotope was determined from the radioautographic optical density.

Calculation of regional blood flow: Kety[4] has shown, by an application of the Fick principle to the conditions of our study, that regional blood flow measured with a biologically inert diffusible tracer substance can be expressed mathematically as:

$$C_i(T) = \lambda_i K_i e^{-K_i T} \int_0^T C_a e^{K_i t} dt \qquad (1)$$

where $C_i(T)$ = the tissue concentration of the tracer substance determined from radioautograms at time T, which in these experiments was 1 minute; λ_i = the tissue-blood partition coefficient for the tracer material, which was assumed to equal 1.00[5]; C_a = the integrated concentration of tracer substance in arterial blood, which is assumed to be variable but equal to 0 at time 0; K_i = the rate of blood flow per unit weight of tissue multiplied by the reciprocal of the partition coefficient.

Because arterial concentration curves of the isotope in these experiments approached a square wave configuration, in an effort to simplify calculations of blood flow, we elected to use a modified form of equation 1, which assumes C_a, the integrated concentration of tracer substance in arterial blood, to be constant,[4] or:

$$C_i(T) = \lambda_i C_a (1 - e^{-K_i T}) \qquad (2)$$

This equation was therefore used to calculate blood flow in different regions of the radioautograms.

Use of the simplified form (equation 2) results in a systematic error of overestimation of flow values compared with values obtained with equation 1. The magnitude of this error

* Kindly provided by Dr. Charles Kennedy of the National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland.

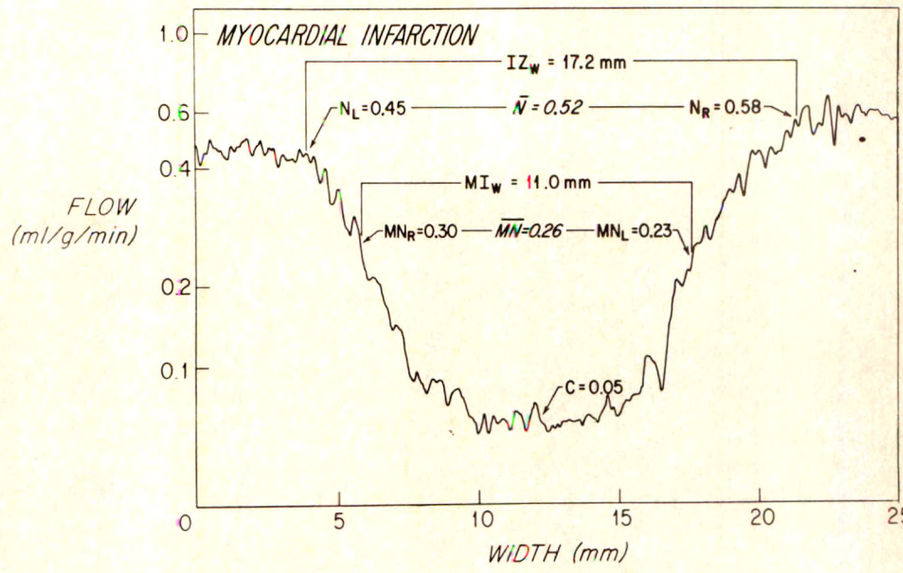

FIGURE 2. Transverse or mid circumferential plane (P_1) photodensitometric scan of the radioautogram shown in Figure 1. C = blood flow at the center of the ischemic zone. IZ_w = width of the ischemic zone; MI_w = width of the zone of myocardial necrosis estimated from adjacent tissue sections; MN_L and MN_R are flow values where myocardial necrosis was first evident on adjacent histologic sections (*MN* represents the mean of two values). N_L and N_R are flow values at left and right normal margins adjacent to the ischemic zone (*N* represents the mean of two values).

based on the observed arterial concentration curves was calculated for a range of flow values (derived with equation 1) similar to those derived with equation 2.[6] Flow values calculated with the latter equation in these experiments were therefore corrected for the appropriate degree of overestimation by means of a graphic method. Flow data were analyzed statistically using a paired *t* test.[7]

Analysis of adjacent histopathologic sections used in the comparison with radioautograms: Ink dots were placed on each tissue section to define a line through which the extent of myocardial necrosis was estimated in the transverse plane (P_1) (lower panel, Fig. 1). Similarly placed ink dots determined the direction of photodensitometric scanning through the corresponding radioautogram (upper panel, Fig. 1). The specific points along this line where predominant myocardial necrosis was first evident on light microscopic study under high power magnification at each margin were determined, and the distance between them was considered to represent the transverse width of the zone of myocardial necrosis (MI_w). Flow values corresponding to these points of myocardial necrosis at each margin (MN) (Fig. 2) could then be read directly from their respective transverse photodensitometric scans. Myocardial cell necrosis at each margin was determined from previously established criteria[8–10] that included more intense eosinophilic staining of myocardial fibers than normal, fiber fragmentation, loss of cross-striations, karyorrhexis, karyolysis, pyknotic nuclei, polymorphonuclear cell infiltration and a marked depletion of stainable glycogen (periodic acid-Schiff sections). At least four of these criteria had to be present to establish the presence of cell necrosis. Tissue sections stained with oil red O, which produced relatively intense staining of neutral fat at each margin of the ischemic zone, were found to be particularly useful as a guide to making these determinations. Comparisons made with hematoxylin-eosin and periodic acid-Schiff sections revealed that myocardial fibers encompassed within this zone of intensely staining lipid material were predominantly normal in histologic appearance and had eosinophilic staining characteristics indistinguishable from those of normal myocardium. In addition, only mild to moderate depletion of stainable glycogen was observed in these fibers as compared with normal fibers and in contrast to the marked depletion of glycogen in necrotic myocardium. Because of these features, dimensional estimates of the extent of myocardial necrosis reported in this study were performed on tissue sections stained with oil red O. Dimensional measurements in millimeters along the transverse line previously defined by the ink dots were made using a calibrated micrographic ruler oriented in parallel with this plane of the tissue section. Measurements were made independently by two observers, and an average value was calculated. Tissue sections in which interobserver differences in dimensional measurements were greater than 1 mm were again reviewed by each observer before an average was calculated. Similar estimates of the extent of myocardial necrosis were made for each section from the endocardial surface to the epicardium (MI_{td}) in the transmural direction (P_2) at 90° to the transverse plane and through the geometric center of the infarct zone.

Results

Illustrative radioautogram: The upper panel of Figure 1 is an example of a radioautogram obtained using the method described. A transmural section of the left ventricular myocardium is shown; the endocardium is above and the epicardium below. The myocardial infarct appears as a pale central zone of markedly diminished flow; the dark areas represent zones of normal myocardium adjacent to the infarct. One can see a gradation of isotope uptake from the homogeneous darker areas at the margins of the myocardial infarction to the pale central zone and another gradation of isotope uptake from the darker epicardial area to the pale central zone and then to a slightly darker area again as the endocardial surface is approached. These flow phenomena were further characterized by photodensitometric scanning first in a transverse or mid circumferential direction through the radioautogram (P_1) and then in a transmural direction from epicardium to endocardium (P_2) (see later).

The lower panel of Figure 1 shows an adjacent tissue section, stained in this instance with oil red O, with a central area of myocardial necrosis circumscribed by a border of intensely staining lipid material.

Profiles of Ischemic Blood Flow

Figure 2 shows a scan obtained by photodensitometric scanning in the transverse plane (P_1). The abscissa indicates millimeters of myocardium and the ordinate represents myocardial blood flow in milliliters per gram of myocardium per minute. These flow values were obtained by converting

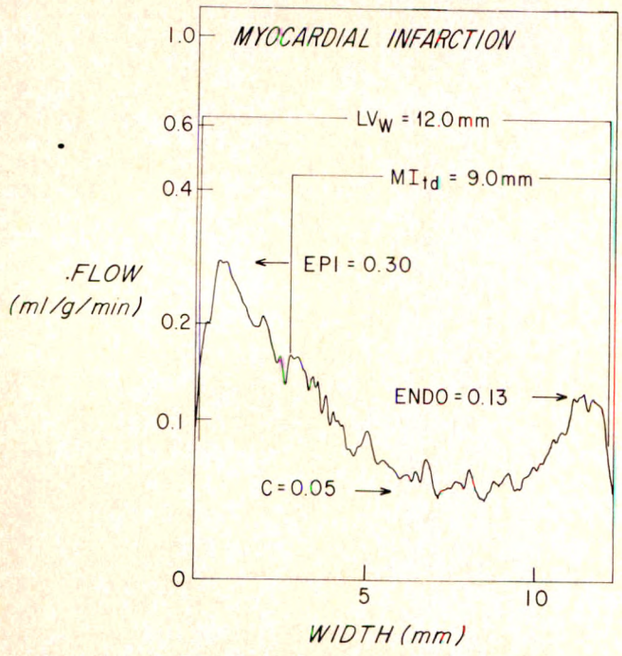

FIGURE 3. Transmural plane (P_2) photodensitometric scan of the radioautogram shown in Figure 1. C, ENDO and EPI, represent, respectively, flow values in the center, endocardium and epicardium of the ischemic zone; LV_W = average transmural thickness of the left ventricular wall encompassing the infarcted region determined from adjacent tissue sections; MI_{td} = transmural dimension of the infarct region estimated from adjacent tissue sections.

directly measured units of optical density derived from photodensitometric scanning to units of myocardial blood flow using the method previously described. As the infarct is traversed from left to right, there is a gradual decrease and subsequent increase in flow, indicating that the margins are not sharp and that there is a gradual diminution of blood flow as the center of the infarct is approached from either margin.

The mean flow value for normal myocardium is indicated by $\overline{N}$ and was obtained by averaging the two normal boundaries adjacent to the infarct zone which in this instance equals 0.52 ml/g per min. Flow in the center of the infarct (C) was taken as the lowest flow value found in the ischemic region, or 0.05 ml/g per min. In all instances, the graphs obtained were quite symmetric, and C was always close to the geometric center of the infarct. In the low flow regions of the tracing, large changes in optical density represent only small increments of flow because of the nonlinearity of the scale.

Figure 3 shows a scan obtained from the experiment previously shown in which the direction of photodensitometric scanning is in the transmural plane (P_2). Again the abscissa indicates millimeters of myocardium and the ordinate milliliters per gram per minute of blood flow. In this plane, scans consistently rendered a flow profile, exhibiting a smooth asymmetric contour. Flow is maximal near the epicardial surface and gradually diminishes to a minimal value in a central area of greatest flow reduction, usually found approximately one third of the distance from the endocardium to the epicardium. From this point, flow increases once again as the endocardial surface is approached.

By combining transverse or mid circumferential (P_1) and corresponding transmural (P_2) photodensitometric scans for each experiment, we could further construct specific profiles of ischemic blood flow within a cubic reference system. Figure 4 graphically illustrates this type of three dimensional construction of blood flow in the ischemic zone and summarizes the results of all seven experiments (Table I). In this model, P_1 (transverse plane) consistently showed a symmetric profile of decreasing blood flow from each normal margin (mean value 0.75 ± 0.11 ml/g per min) to the center of the myocardial infarct (mean 0.08 ± 0.02 ml/g per min or 11.7 ± 3.5 percent of normal flow), whereas P_2 (transmural plane) showed an asymmetric profile of decreasing blood flow from the epicardium (mean value 0.36 ± 0.06 ml/g per min) to the center of the infarct and a subsequent but significant increase to 0.22 ± 0.03 ml/g per min near the endocardial surface. Endocardial to epicardial flow ratios in ischemic myocardium averaged 0.84 ± 0.32, indicating more severe flow deprivation in the endocardial half as than in the epicardial half of the left ventricular shell.

In comparison, transmural photodensitometric scans of normal left ventricular myocardium (Table I) showed relatively flat profiles of blood flow with slightly greater endocardial (mean 0.64 ± 0.13 ml/g per min) than epicardial (mean

TABLE I
Regional Myocardial Blood Flow (ml/g per min) in Normal and Ischemic Myocardium Comparing Results Obtained From Transverse and Transmural Plane Photodensitomeric Scans

	Transverse Plane (P_1)					Transmural Plane (P_2)				
						Ischemic Zone		Normal Myocardium		
Exp. no.	$\overline{N}$	$\overline{MN}$	$(\overline{N} - \overline{MN})/N \times 100$ (%)	C	(C/N) × 100 (%)	EPI	ENDO	LV EPI	LV ENDO	LV MN
1	1.315	0.566	56.96	0.096	7.30	0.264	0.178	1.203	1.260	1.232
2	0.589	0.325	44.82	0.133	22.58	0.538	0.302	0.570	0.429	0.500
3	0.547	0.302	44.79	0.145	26.51	0.547	0.255	0.353	0.500	0.427
4	0.516	0.261	49.42	0.050	9.69	0.296	0.133	0.513	0.513	0.513
5	0.977	0.475	51.38	0.043	4.40	0.091	0.247	...	...	...
6	0.655	0.447	31.76	0.061	9.31	0.426	0.139	0.527	0.563	0.545
7	0.647	0.404	37.56	0.014	2.16	0.352	0.252	0.494	0.586	0.540
Mean	0.749	0.397	45.24	0.077	11.71	0.359	0.215	0.610	0.642	0.626
± SEM	0.11	0.04	3.2	0.018	3.5	0.06	0.03	0.12	0.13	0.12

* Statistical analyses: Significant differences (probability [P] <0.05, paired observations) are observed for $\overline{N}$ versus $\overline{MN}$, $\overline{N}$ versus C, $\overline{MN}$ versus C, ischemic zone EPI versus ENDO and $\overline{N}$ versus LVM; LV EPI and LV ENDO do not differ significantly (P >0.05).

C = center of ischemic zone; C/$\overline{N}$ × 100 percent = degree of blood flow reduction at center of ischemic zone; ENDO = endocardium; EPI = epicardium; Exp. = experiment; LV = left ventricular; LVM = average of epicardial and endocardial flow in normal left ventricular myocardium; $\overline{MN}$ = average flow value at the point when myocardial necrosis was first evident in adjacent tissue sections; $\overline{N}$ = average flow value in normal margins adjacent to ischemic zone; $(\overline{N} - \overline{MN})/\overline{N} \times 100$ (%) = degree of blood flow reduction from normal related to myocardial necrosis; SEM = standard error of the mean.

TABLE II

Transverse and Transmural Plane Dimensions of the Zone of Myocardial Infarction, Ischemic Zone and Border Zone

Exp. no.	MI_w (mm)	IZ_w (mm)	BZ_w (mm)	MI_{td} (mm)	LV_w (mm)	$(BZ_w/IZ_w) \times 100$ (%)	$(MI_w/IZ_w) \times 100$ (%)	$(V_{MI}/V_{IZ}) \times 100$ (%)* Truncated	Bitruncated	Ellipsoid	Cylinder
1	6.0	9.3	3.3	11.0	11.0	35.5	64.5	†	26.8	41.6	41.6
2	6.5	9.8	3.3	10.0	11.5	33.7	66.3	†	29.2	38.3	38.3
3	9.5	15.3	5.8	7.0	13.0	37.9	62.1	21.3	24.7	18.1	20.9
4	11.0	17.2	6.2	9.0	12.0	36.0	64.0	30.6	29.8	36.0	30.7
5	11.5	16.7	5.1	11.0	13.0	30.5	68.9	37.0	35.0	49.3	40.0
6	15.5	19.2	3.7	9.0	13.0	19.3	80.7	49.8	58.9	38.8	45.3
7	16.0	19.8	3.8	13.0	13.0	19.8	80.8	65.9	59.3	80.7	65.3
Mean	10.9	15.3	4.5	10.0	12.4	30.4	69.6	40.9	37.7	43.3	40.3
± SEM	±1.5	±1.6	±0.5	±0.7	±0.3	±3.0	±3.0	±7.7	±5.7	±7.2	±5.2

* Infarct size in relation to the magnitude of the ischemic zone (V_{MI}/V_{IZ}) (%) is calculated assuming four different geometric models.
† Calculations could not be performed using these models because of unusual infarct configurations in these experiments.
BZ_w = border zone ($IZ_w - MI_w$ in the transverse plane); $BZ_w/IZ_w \times 100$ (%) and $MI_w/IZ_w \times 100$ (%) = BZ_w and MI_w expressed as percent of IZ_w; IZ_w = width of the ischemic zone determined in transverse photodensitometric scans; LV_w = average transmural left ventricular wall thickness; MI_{td} = transmural dimension of the zone of myocardial necrosis estimated from tissue sections; MI_w = transverse width of the zone of myocardial necrosis estimated from adjacent histologic sections; SEM = standard error of the mean; $(V_{MI}/V_{IZ}) \times 100$ (%) = infarct size expressed as percent of ischemic zone magnitude assuming four different geometric models.

0.61 ± 0.12 ml/g per min) flow values. However, these values were not significantly different from each other. Left ventricular mean flow (mean 0.63 ± 0.12 ml/g per min) was computed by averaging left ventricular endocardial and epicardial flow values. Endocardial to epicardial flow ratios in normal myocardium averaged 1.08 ± 0.09 and did not differ significantly from unity.

Values for blood flow at the normal margins of the infarct zone in the transverse plane ($\overline{N}$) were slightly but significantly greater than corresponding values for left ventricular mean flow (Table I), suggesting that the infarct margins were hyperemic.

Comparison of magnitude of reduction of regional blood flow and histopathologic evidence for myocardial necrosis: In the next phase of this comparative analysis, we determined the specific values of blood flow from photodensitometric scans in the transverse plane at the corresponding point at which myocardial necrosis was first evident in adjacent histopathologic tissue sections (Table I). Values for this determination ($\overline{MN}$) ranged from 0.26 to 0.57 ml/g per min (mean 0.40 ± 0.04 ml/g per min, representing an average reduction in blood flow of 45.2 ± 3.2 percent from normal values. This degree of flow reduction therefore permits more accurate definition of a border zone of intermediate flow reduction located immediately outside the region of myocardial necrosis where cell viability is maintained at 24 hours.

Quantification of border zone dimensions: In an effort to characterize a border zone of intermediate flow reduction and determine a quantitative measurement of its width, in the second part of this study we undertook a systematic comparison between the total width of the ischemic zone of flow reduction (IZ_w) determined with radioautography in the

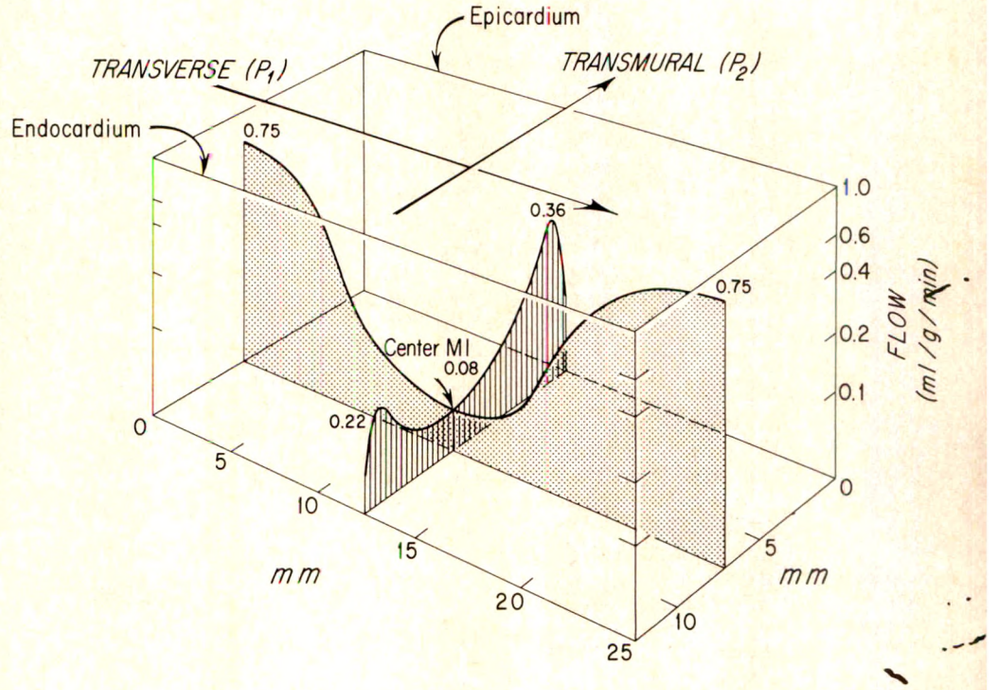

FIGURE 4. Schematic reconstruction of profiles of ischemic blood flow based upon transverse (P_1) and transmural plane (P_2) photodensitometric scans combined in a three-dimensional reference system. Flow values shown for normal margins, epicardium, endocardium, and infarct center (Center MI) represent mean values for seven experiments.

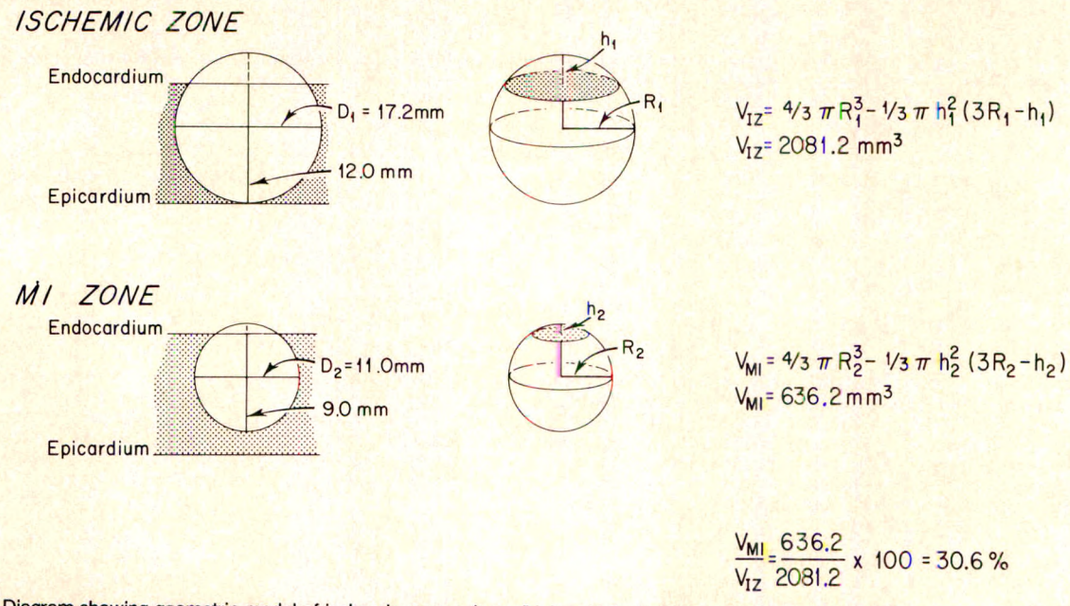

FIGURE 5. Diagram showing geometric model of ischemic zone volume (V_{IZ}) and infarct (MI) zone volume (V_{MI}) based upon a truncated spheroid from a single experiment. D_1 = ischemic zone width (IZ_w) measured from a transverse plane (P_1) photodensitometric scan; $h_1 = D_1$ minus transmural left ventricular wall thickness (LV_w); $R_1 = D_1/2$. The ischemic zone sphere was assumed to be tangent to the epicardial surface. To calculate the volume of the myocardial infarct zone (V_{MI}), both transverse (D_2 or MI_w) and transmural (MI_{td}) dimensions were measured from adjacent tissue sections. $h_2 = D_2$ minus transmural dimension of the infarct zone (or MI_{td}). The mathematical formulas used and the calculation of V_{MI}/V_{IZ} (in percent) in this experiment are indicated. (See appendix for details.)

transverse plane and the corresponding width of the zone of myocardial necrosis (MI_w) as estimated from adjacent histopathologic sections (Table II). Values for ischemic zone width (IZ_w) determined with radioautography ranged from 9.3 to 19.8 mm (mean 15.3 ± 1.6 mm); corresponding values for width of the zone of myocardial necrosis (MI_w), as estimated from adjacent histopathologic sections, ranged from 6.0 to 16.0 mm (mean 10.9 ± 1.5 mm or 69.6 ± 3.0 percent of IZ_w). Border zone width (BZ_w) in the transverse plane, obtained by subtracting the width of the myocardial infarct zone from that of the ischemic zone, ranged from 3.3 to 6.2 mm (mean 4.5 ± 0.5 mm or 30.4 ± 3.0 percent of ischemic zone width).

Quantification of infarct size in relation to magnitude of ischemic zone: To obtain further quantitative characterization of the size of the infarct and its relation to the size of the total zone of ischemic blood flow reduction, we undertook a systematic comparison of both transverse and transmural dimensions of the total ischemic zone determined with radioautography and the corresponding dimensions of the zone of myocardial necrosis as estimated from adjacent histopathologic sections. In this analysis, we assumed truncated spheroidal models situated within the wall of the left ventricle to represent closely the volume configurations of both the zone of ischemic blood flow reduction and the zone of myocardial necrosis.

Figure 5 shows an example of such a volume calculation using the formulas indicated. This shows that infarct size (V_{MI}) is 30.6 percent of the total size of the ischemic zone of blood flow reduction (V_{IZ}). With this geometric model, the average value for this determination in all experiments was 40.9 ± 7.7 percent. For comparison, however, we extended these calculations, assuming different geometric models to approximate infarct size and the size of the total zone of ischemic blood flow reduction (see Appendix). The data for this comparison are summarized in Table II.

Thus, assuming a bitruncated spheroid where the ischemic and infarct zone centers are considered equidistant from their respective epicardial and endocardial surfaces, the average value for percent V_{MI}/V_{IZ} of 37.7 ± 5.7 percent is similar but slightly lower than that for a singly truncated spheroidal model. Average values for this determination assuming either ellipsoidal or cylindrical models (mean 43.3 ± 7.2 and 40.3 ± 5.2 percent, respectively) are not significantly different from these values.

Discussion

Measurements of regional blood flow in ischemic myocardium: Acute coronary occlusion in experimental animals consistently produces a focal zone of myocardial ischemia characterized by several regional mechanical, electrocardiographic, biochemical and flow derangements.[11] Regional myocardial blood flow in such animal models has previously been studied by investigators utilizing various techniques.[12–23] Most such studies show similar findings: (1) significant reduction of flow from normal values in ischemic or infarcted myocardium; (2) most severe flow reduction at the center of the ischemic zone and also in the subendocardial half of the transmural thickness of the left ventricular wall; (3) intermediate levels of flow reduction at the margins of the ischemic zone and subepicardium; and (4) a decrease in the ratio of endocardial to epicardial blood flow indicating flow redistribution.

Our findings are in close agreement with these observations (Fig. 2 and 3, Table I). Furthermore, by combining transverse and transmural photodensitometric scans, the profiles of ischemic blood flow could be characterized schematically in a three dimensional or cubic reference system (Fig. 4). Thus, photodensitometric scans in the transverse or mid circumferential

plane consistently showed symmetric profiles of diminishing blood flow from each normal margin to the center of the infarct. Values for blood flow at the infarct center (C, Table I) varied considerably, but in each instance they were markedly lower than corresponding values in adjacent normal myocardium. Corresponding photodensitometric scans in the transmural plane showed an asymmetric profile of decreasing blood flow from the epicardium to the infarct center with a subsequent slight but significant increase as the endocardial surface was approached. A possible explanation for this finding may be the passive influx of radioisotope by way of the endomural coronary collateral circulation (that is, arterioluminal and arteriosinusoidal vessels) near the endocardial surface, as previously suggested by Moir.[24] However, it is unlikely that contamination from luminal blood alone would account for this consistent finding in transmural photodensitometric scans. Under conditions of ischemia, Moir found that the magnitude of contamination from luminal blood was only approximately 0.5 ml/100 g of myocardium and that the specific sites of increased contamination were highly variable, that is, the number of sites with greater endocardial than epicardial, contamination nearly equalled that of sites with greater epicardial than endocardial contamination.

Potential sources of error: Although the specific values for regional blood flow in ischemic myocardium observed in our study 24 hours after coronary ligation are comparable with those reported by others utilizing different techniques, in the presence of myocardial ischemia, the validity of nearly all such regional flow measurements, regardless of the method used, remains uncertain,[17] as does the validity of the assumptions on which such determinations are based.[25] In this context, several potential sources of error that are relevant to our study require further comment. For the purposes of simplification, flow calculations were performed using a modification of the Kety equation[4] (equation 2), which introduces a systematic error of overestimation of flow values that requires correction.[6] The tissue-blood partition coefficient for antipyrine used to calculate flow in these experiments was assumed to be 1.00. Although this value may be an accurate approximation for normal myocardium under resting hemodynamic conditions,[5] the actual partition coefficient for ischemic myocardium under these experimental conditions is unknown and may represent a source of error in these flow determinations.[17]

Additional errors may have been introduced as a result of the effect of unequilibrated arterial blood on tissue antipyrine concentrations and the lack of correction for the smearing effect of transport function of the sampling catheter.[17] However, this latter source of error was minimized by using a relatively short (10 cm) polyethylene catheter for sampling arterial blood samples.

In our analysis of tissue sections, dimensional measurements of the extent of myocardial necrosis were made only in single defined transverse and transmural planes or lines that could be compared with corresponding radioautograms. Because considerable interdigitation of fibers occurs at the transitions from normal to ischemic and from ischemic to necrotic zones, such measurements can be considered only estimates rather than precise dimensions of these zones. Nevertheless, these estimates permitted some degree of quantification of infarct size relative to the magnitude of the ischemic zone.

Magnitude of ischemic blood flow reduction and myocardial necrosis: In the comparative analysis between transverse photodensitometric scans and adjacent tissue sections, we found that specific values for regional blood flow corresponding to the point at which myocardial necrosis was first evident varied considerably among experiments (0.26 to 0.57 ml/g per min) (Table I). However, each determination represented a level of flow reduction from its corresponding normal value, which was comparable with the average value reported for all experiments (45.2 ± 3.2 percent). These data therefore represent independent confirmation with a new technique of previous observations of others regarding the levels of blood flow reduction required to produce objective evidence for regional myocardial ischemia[11] and myocardial infarction.[26] Furthermore, this technique may permit better resolution between specific flow measurements and myocardial necrosis than is usually provided with microsphere or other techniques that require multiple tissue biopsies to reconstruct flow profiles in the ischemic region. The present method provides a continuous graphical representation of ischemic blood flow that can be compared with histopathologic findings in adjacent regions.

Infarct size and border zone: After sustained coronary occlusion, the ischemic zone presumably contains various amounts of both irreversibly and reversibly injured cells.[27] This is likely to be true because subsequent myocardial necrosis is not completely uniform throughout this region, as frequently manifested by the subepicardial sparing of myocardial tissue. Most probably the magnitude of the ischemic injury and ultimately the extent of myocardial necrosis that results is a highly dynamic process related in a complex manner to several mechanical[28,29] and time-dependent flow factors.[16,18,30]

In this study, we attempted to quantify infarct size (V_{MI}) in relation to the magnitude of its corresponding ischemic zone (V_{IZ}). Average calculated values for V_{MI}/V_{IZ} in percent were remarkably similar for all four geometric models (Table II). These data indicate that in small focal myocardial infarcts, the extent of myocardial necrosis in geometric terms encompasses approximately 40 percent of the total ischemic zone. These findings further suggest that a substantial region of cell viability is maintained at 24 hours after coronary occlusion.

The presence of a "border zone" at the periphery of an ischemic zone produced by acute coronary occlusion has previously been identified by investigators using a variety of study techniques. These include studies employing differential histochemical staining methods examined with light microscopy,[31] electron microscopic studies,[32] polarographic determinations of intramyocardial oxygen concentration,[33] epicardial electrocar-

diograms (S-T segment depression),[34] studies of segmental mechanical function[35,36] and measurements of regional blood flow.[18,19] The absolute magnitude of this border zone of jeopardized but potentially viable myocardium is not known, but recent studies suggest that it may be substantial and furthermore may be influenced by a number of hemodynamic, metabolic and pharmacologic interventions.[28]

In our study the mean width of the border zone was 4.5 ± 0.5 mm or 30.4 ± 3.0 percent of the width of the ischemic zone. If one assumes that the mass of both the infarct and ischemic zones are represented by cylindrical models within the left ventricular shell, the border zone averaged approximately 60 percent of the ischemic zone mass (Table II) for small focal myocardial infarcts characterized in these experiments. However, if one assumes a constant border zone width (4.5 mm) and calculates its size for myocardial infarcts of progressively increasing diameter (Fig. 6), the border zone would comprise 36, 32, 29 and 28 percent of ischemic zone mass for infarct sizes of 10, 25, 40 and 50 g, respectively. On the basis of these calculations, the contribution of the border zone, although increasing in absolute magnitude, constitutes a progressively smaller part of total ischemic zone mass until a near steady value is reached at larger infarct sizes. These theoretical calculations, although unconfirmed, should be taken into account when studying interventions aimed at maintaining myocardial viability.

Our findings of a border zone of intermediate flow reduction 24 hours after coronary occlusion are quite consistent with previous observations made by Schaper and Pasyk[18] and other investigators[19] using different techniques of flow measurement. However, they are in marked contrast with the results of other studies[37,38] made of the early phases of acute ischemic injury. In the latter, tissue supplied by the occluded artery was delineated by dye injection, and ischemic myocardium was separated from nonischemic tissue by dissection along a stained border. Because of uncertainties in this separation technique, flow supplied by vessels adjacent to the ischemic zone was determined by microspheres injected during perfusion of the vessel to be occluded with unlabeled blood. After coronary occlusion, regional blood flow in normal and ischemic regions was measured by a second injection of microspheres. Intermediate values of blood flow obtained from samples in the zone of transition from normal to ischemic myocardium suggested, when corrected for collateral flow from adjacent vessels, that the degree of flow reduction at the periphery of the ischemic zone was nearly equal to that at the center. These findings were noted both immediately and 2 hours after coronary occlusion. In work using a similar approach,[38] creatine kinase depletion tended to be uniform throughout the ischemic zone.

In our study, we did not attempt to delineate the tissue specifically perfused by the occluded vessel because this would have made subsequent histopathologic study of tissues impossible. Furthermore, determination of blood flow derived exclusively from collateral vessels was not possible with the radioautographic technique

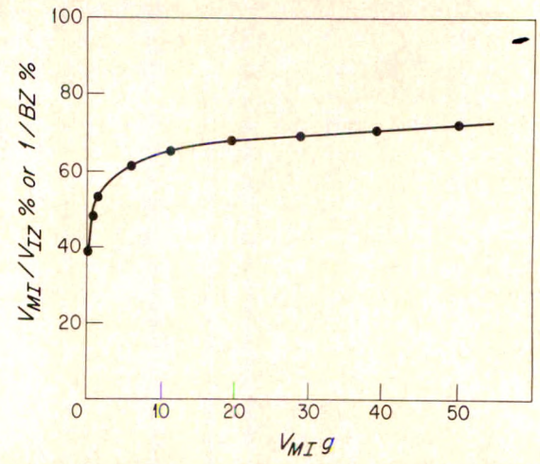

FIGURE 6. Theoretical plot of infarct size (V_{MI}) in relation to the ratio of V_{MI}/V_{IZ} (percent) or 1/BZ (percent) assuming a constant border zone width (BZ_w) and progressively increasing values for width of infarct zone. The mass of both the infarct (MI) and ischemic (IZ) zones are assumed to be represented by cylindrical models within the left ventricular wall where ischemic zone depth, h_1, equals the average transmural thickness of the left ventricular wall, LV_w (12.4 mm), and infarct zone depth, h_2, equals the average transmural dimension of the infarct zone (MI_{td}) (10.0 mm) (see appendix). On the basis of these calculations, the contribution of the border zone, although increasing in absolute magnitude, constitutes a progressively smaller part of total ischemic zone mass until a near steady value is reached at larger infarct sizes.

used. Presumably, the time-dependent development of collateral blood flow, as well as redistribution of flow within the ischemic region,[16,18,30] may account for our observations of a zone of intermediate flow reduction where cell viability maintained 24 hours after coronary occlusion.

Acknowledgment

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Appendix

Volume calculations and assumptions were made for four geometric models considered to represent infarct size (V_{MI}) and the total magnitude of the ischemic zone of blood flow reduction (V_{IZ}):

Truncated spheroid: An example of this calculation and the formulas used is shown in Figure 5. In these calculations, the ischemic zone sphere was assumed to be tangent to the epicardial surface, whereas the depth of the infarct sphere was determined by the transmural dimension of the infarct zone (MI_{td}). The geometric centers of the spheres, although in the same transmural plane, were therefore eccentrically located with respect to each other.

Bitruncated spheroid: With use of this model, the geometric centers of both the ischemic and infarct zone spheres were considered to be equidistant from their respective epicardial and endocardial surfaces, that is, at the left ventricular mid circumference. *For the ischemic zone:*

$R_1 = \frac{D_1}{2}$ where D_1 = ischemic zone width (IZ_w)

and

$h_1 = D_1 -$ transmural left ventricular wall thickness (LV_w)/2.

For the infarct zone:

$$R_2 = \frac{D_2}{2} \text{ where } D_2 = MI_w \text{ and } h_2 = D_2 - LV_w/2.$$

In contrast to calculations for truncated spheroid, MI_{td} was not used in these calculations. Volume = $4/3\pi R^3 - 2/3\pi h^2(3R - h)$.

Ellipsoid: In these calculations, for the ischemic zone, D_1 or IZ_w and LV_w were assumed to represent the major (b_1) and minor (a_1) hemiaxes, respectively, of a prolate ellipsoid. Similarly, for the infarct zone, D_2 or $MI_w = b_2$ and $MI_{td} = a_2$. Volume = $\pi/6 \times a^2 \times b$.

Cylinder: With this model, for the ischemic zone, $R_1 = IZ_w/2$ and the ischemic zone depth, $h_1 = LV_W$. For the infarct zone, $R_2 = MI_w/2$ and the infarct depth, $h_2 = MI_{td}$. Volume = $\pi R^2 h$.

References

1. **Reivich MJ, Jehle J, Sokoloff L, et al:** Measurement of regional cerebral blood flow with antipyrine-C^{14} in awake cats. J Appl Physiol 27:296–300, 1969
2. **Malsky PM, Vokonas PS, Paul SJ, et al:** Autoradiographic measurement of regional blood flow in normal and ischemic myocardium. Am J Physiol 232:H576–H583, 1977
3. **Vokonas PS, Pirzada FA, Hood WB Jr:** Experimental myocardial infarction. XII. Dynamic changes in segmental mechanical behavior of infarcted and noninfarcted myocardium. Am J Cardiol 37: 853–859, 1976
4. **Kety SS:** I. Blood-tissue exchange methods: theory of blood-tissue exchange and its application to measurement of blood flow. Methods Med Res 8: 223–235, 1960
5. **Krasnow N, Levine HJ, Wagman RJ, et al:** Coronary blood flow measured by I^{131} iodo-antipyrine. Circ Res 12:58–62, 1963
6. **Aronow S:** Personal communication, January 7, 1977
7. **Snedecor GW:** Statistical Methods Applied to Experiments in Agriculture and Biology, fifth edition. Ames, Iowa, Iowa State University Press, 1956, p 49
8. **Mallory GK, White PD, Salcedo-Salgar J:** The speed of healing of myocardial infarction. Am Heart J 18:647–671, 1939
9. **Kent SP, Diseker M:** Early myocardial ischemia: study of histochemical changes in dogs. Lab Invest 4:398–405, 1955
10. **Yokohama HO, Jennings RB, Clabaugh GF, et al:** Histochemical studies of early experimental myocardial infarction. Arch Pathol (Chicago) 59:347–354, 1955
11. **Scheuer J, Brachfeld N:** Coronary insufficiency: relations between hemodynamic, electrical and biochemical parameters. Circ Res 18:178–189, 1966
12. **Fortuin NJ, Kaihara S, Becker LC, et al:** Regional myocardial blood flow in the dog studied with radioactive microspheres. Cardiovasc Res 5:331–336, 1971
13. **Marcus ML, Kerber RE, Ehrhardt J, et al:** Three dimensional geometry of acutely ischemic myocardium. Circulation 52:254–263, 1975
14. **Bishop PS, White FC, Bloor CM:** Regional myocardial blood flow during acute myocardial infarction in the conscious dog. Circ Res 38:429–438, 1976
15. **Rivas F, Cobb FR, Bache RJ, et al:** Relationship between blood flow to ischemic regions and extent of myocardial infarction: serial measurement of blood flow to ischemic regions in dogs. Circ Res 38: 439–477, 1976
16. **Hirzel HO, Nelson GR, Sonnenblick EH, et al:** Redistribution of collateral blood flow from necrotic to surviving myocardium following coronary occlusion in the dog. Circ Res 39: 214–222, 1976
17. **Utley J, Carlson EL, Hoffman JIE, et al:** Total and regional myocardial blood flow measurements with 25μ, 15μ, 9μ and filtered 1–10μ diameter microspheres and antipyrine in dogs and sheep. Circ Res 34:391–405, 1974
18. **Schaper W, Pasyk S:** Influence of collateral flow on the ischemic tolerance of the heart following acute and subacute coronary occlusion. Circulation 53: Suppl I:I-58–I-62, 1976
19. **Beller GA, Smith TW, Hood WB Jr:** Altered distribution of tritiated digoxin in the infarcted canine left ventricle. Circulation 56: 572–579, 1972
20. **Chimoskey JE, Szentivanyi M, Zakheim R, et al:** Temporary coronary occlusion in conscious dogs: collateral flow and electrocardiogram. Am J Physiol 212:1025–1032, 1967
21. **Rees JR, Redding VJ:** Experimental myocardial infarction in the dog. Comparison of myocardial blood flow within, near, and distant from the infarct. Circ Res 25:161–170, 1969
22. **Shaw DJ, Pitt A, Friesinger GC:** Autoradiographic study of the ^{133}xenon disappearance method for measurement of myocardial blood flow. Cardiovasc Res 6:268–276, 1971
23. **Cohn PF, Kirk ES, Downey JM, et al:** Autoradiographic evaluation of myocardial collateral circulation in the canine heart. Cardiovasc Res 7:181–185, 1973
24. **Moir T:** Study of luminal coronary collateral circulation in the beating canine heart. Circ Res 24:735–744, 1969
25. **Zierler KL:** Equations for measuring blood flow by external monitoring of radioisotopes. Circ Res 16:309, 1965
26. **Brachfeld N:** Maintenance of cell viability. Circulation 50: Suppl IV:IV-202–IV-215, 1969
27. **Jennings RB:** Early phase of acute myocardial ischemic injury and infarction. Am J Cardiol 24:753–765, 1969
28. **Maroko PR, Kjekshus JK, Sobel BE, et al:** Factors influencing infarct size following experimental coronary artery occlusion. Circulation 43:67–82, 1971
29. **Brown BG, Gundel WD, Gott VL, et al:** Coronary collateral flow following acute coronary occlusion: a diastolic phenomenon. Cardiovasc Res 8:621–631, 1974
30. **Marcus ML, Kerber RE, Ehrhardt J, et al:** Effects of time on the volume and distribution of coronary collateral flow. Am J Physiol 230:279–285, 1976
31. **Cox JL, McLaughlin VW, Flowers NC, et al:** The ischemic zone surrounding acute myocardial infarction. Its morphology as detected by dehydrogenase staining. Am Heart J 76: 650–659, 1968
32. **Herdson PB, Sommers HM, Jennings RB:** A comparative study of the fine structure of normal and ischemic myocardium with special reference to early changes following temporary occlusion of a coronary artery. Am J Pathol 46:367–386, 1965
33. **Sayen JJ, Sheldon WF, Horwitz O, et al:** Studies of coronary disease in the experimental animal. II. Polarographic determinations of local oxygen availability in the dog's left ventricle during coronary occlusion and pure oxygen breathing. J Clin Invest 30:932–940, 1951
34. **Kjekshus JK, Maroko PR, Sobel BE:** Distribution of myocardial injury and its relation to epicardial ST-segment changes after coronary artery occlusion in the dog. Cardiovasc Res 6:490–499, 1972
35. **Puri S:** Modification of experimental myocardial infarct size by cardiac drugs. Am J Cardiol 33:521–528, 1974
36. **Theroux P, Franklin D, Ross J Jr, et al:** Regional myocardial function during acute coronary occlusion and its modification by pharmacologic agents in the dog. Circ Res 35:896–908, 1974
37. **Fischl SJ, Sonnenblick EH, Kirk ES:** Absence of a border ischemic zone following acute coronary occlusion (abstr). Circulation 50: Suppl II:II-172, 1974
38. **Hirzel HO, Sonnenblick EH, Kirk ES:** Uniformity of creatine phosphokinase-depletion in ischemic myocardium 24 hours after coronary occlusion (abstr). Am J Cardiol 37:143, 1976

Effects of Tocainide on Ventricular Fibrillation Threshold

Comparison With Lidocaine

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Right ventricular epicardial ventricular fibrillation threshold was determined during paced supraventricular rhythm using 100 hertz trains of stimuli at 15 minute intervals in dogs before, during and after a 90 minute infusion of tocainide, an orally effective antiarrhythmic drug. With each ventricular fibrillation threshold determination, simultaneous blood samples were obtained for determination of drug concentration. Concentration-response curves for dogs receiving tocainide showed that in general there is no measurable increase in ventricular fibrillation threshold at concentrations of less than 6 to 10 μg/ml. At 10 μg/ml the mean ventricular fibrillation threshold increased 28 percent (range 14 to 67 percent), at 15 μg/ml 53 percent (range 28 to 111 percent) and at 20 μg/ml 71 percent (range 37 to 143 percent). There was a wide range of interanimal sensitivity to tocainide, but for each animal there was a significant relation between increase in ventricular fibrillation threshold and log plasma concentration.

Similar observations for lidocaine revealed that in general there was no measurable effect below 1.3 to 4 μg/ml, a 77 percent mean increase (range 2 to 146 percent) at 4 μg/ml, a 136 percent mean increase (range 55 to 235 percent) at 6 μg/ml and a 177 percent mean increase (range 76 to 299 percent) at 8 μg/ml. Tocainide also increased the ventricular fibrillation threshold during induced premature ventricular beats. In this model, tocainide significantly increased ventricular fibrillation threshold; however, this increase was less than that observed at clinically tolerated lidocaine plasma concentrations.

Tocainide, a primary amine analog of lidocaine, has recently undergone a series of evaluations in man to determine its pharmacokinetic and antiarrhythmic properties.[1–3] Tocainide has linear pharmacokinetics, a half-life of approximately 13 hours and almost 100 percent bioavailability when given orally. After single large oral doses[3] and multiple oral doses,[1] tocainide effectively suppresses ventricular ectopic complexes. Its antiarrhythmic activity is related to plasma drug concentration in individual patients and in groups. Although there is a wide range of individual patient response to tocainide, for a group of patients suppression of ventricular ectopic complexes generally occurs at plasma concentrations greater than 6 μg/ml.[1,4] Because tocainide may have potential application for prevention of sudden arrhythmic death in patients at risk of ventricular fibrillation, we attempted to determine the effects of tocainide on the ventricular fibrillation threshold, using an animal model. In addition, we attempted to determine if any observed effect on the ventricular fibrillation threshold could be related to plasma drug concentration and to compare tocainide with the well studied antiarrhythmic agent lidocaine.

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Methods

Experimental Procedures

Dog preparation: Twenty-nine healthy fasting mongrel dogs weighing 16.4 to 25.5 kg were anesthetized with intravenous sodium pentobarbital at a dose of 30 mg/kg. The animals were intubated with a cuffed endotracheal tube and ventilated with humidified room air, using a Harvard pump. A large bore catheter was inserted into the left femoral artery to monitor the systemic arterial pressure, using a Statham P23 Db transducer; mean aortic pressure was derived electronically. Blood samples for arterial blood gas analysis were drawn throughout the experiment and were analyzed using a Corning model 165 blood gas analyzer. Depth and rate of respiration were adjusted to maintain arterial partial pressure of oxygen (PO_2) at more than 72 mm Hg and pH between 7.35 and 7.44 throughout the experiment. A catheter was placed in the right femoral vein for administration of additional anesthetic agent, which was given to maintain deep anesthesia throughout the experiment. The right jugular vein was catheterized for drug infusions. The chest was opened by means of a mid-line sternotomy and the heart exposed and supported in a pericardial sling. The sinus node was mechanically crushed and a bipolar pacemaker electrode attached to the right atrium. Atrial pacing at a rate of 150 beats/min (cycle length 400 msec) was maintained using one channel of a Grass model S88 stimulator and an isolation unit.

Ventricular fibrillation thresholds: These thresholds were determined using a modification of the method described by Moore et al.[5] A fibrillation electrode was sutured to the right ventricular epicardial surface. This electrode consisted of bipolar platinum electrodes, each with a diameter of 1.5 mm, embedded 10 mm apart in acrylic plastic. The fibrillating current was delivered using specially designed digital timing circuitry and a Grass S88 stimulator with a constant current device. Fibrillating currents were introduced after every 12th paced supraventricular beat. The fibrillating current was configured as a train of 16 square wave pulses, 4 msec in duration at a frequency of 100 hertz. The two supraventricular paced beats after each fibrillation train were inhibited. Lead II of the electrocardiogram and a right ventricular electrogram recorded from the region of the fibrillation electrode were continuously monitored. The fibrillating train was timed so that it spanned the entire vulnerable period of the cardiac cycle, with the train ending approximately 30 msec beyond the T wave of the local electrogram. The current delivered to the fibrillation electrodes was continuously monitored as the voltage drop across a precision (±1 percent) 100 ohm resistor and displayed on a Tektronics storage oscilloscope. The current delivered to the ventricle was increased in 0.5 to 1 milliampere increments until ventricular fibrillation occurred. The minimal level of current producing sustained ventricular fibrillation was defined as the ventricular fibrillation threshold. Each threshold determination was recorded on a model SP 700 Ampex tape recorder and was subsequently printed on a Honeywell model 1508 visicorder oscillograph to confirm that the fibrillating train was in the correct position. The heart was directly defibrillated within 10 seconds using 10 to 15 watt seconds delivered from a Hewlett-Packard model 780 2C defibrillator delivered through 5 cm paddles applied directly to the heart. Ventricular fibrillation threshold was measured at 15 minute intervals throughout the study.

During some experiments the fibrillation threshold was determined for artificially induced premature ventricular complexes. A single 4 msec square wave stimulus was placed during diastole using a bipolar electrode sutured to the left ventricle. Stimulus strength was increased in intensity until threshold for a premature complex was obtained. Stimulus strength was then increased to twice diastolic threshold, and the stimulus was moved into the relative refractory period of the preceding paced supraventricular complex as far as possible to still achieve reliable capture. The stimulus was then increased to 1.5 milliamperes and left at that level for the duration of the experiment. A train of twelve 4 msec square wave pulses at 100 hertz was then introduced across the T wave of the premature ventricular complex by means of a right ventricular electrode, and ventricular fibrillation threshold was determined as described.

Drugs: These were administered by continuous infusion over a 90 minute period using a Harvard infusion pump. Blood samples for drug concentrations were obtained with use of the left femoral arterial catheter each time ventricular fibrillation was induced and were replaced with a like volume (5 cc) of normal saline solution. Plasma drug concentrations for tocainide were determined using a high pressure liquid chromatographic assay.[6] Lidocaine was measured using a gas chromatographic method.[7]

Experimental Protocol

Group 1 (control group): Ten dogs were studied to evaluate the stability of the preparation throughout the duration of the experiment. Ventricular fibrillation threshold in these 10 animals was determined every 15 minutes for 270 minutes. Seven of these animals were studied without placebo infusions. Three additional control animals given saline infusion were interspersed with the animals receiving drug infusion. The investigators performing the ventricular fibrillation study did not know whether they were giving drug or saline infusion. For each of these 10 control animals, the average ventricular fibrillation threshold, the standard deviation and coefficient of variation were calculated.

For the tocainide and lidocaine infusions (Groups 2 to 4), each animal served as its own control. Before drug infusion in each experiment four consecutive control measurements of ventricular fibrillation threshold, within ±1 milliampere for supraventricular complexes and ±2 milliamperes for premature ventricular complexes, were obtained. The average of these four values was taken as the control ventricular fibrillation threshold for that animal.

Group 2 (variable tocainide infusion): Ten animals were studied in this group. Fibrillation threshold was determined during paced supraventricular beat complexes in five animals and during premature ventricular complexes in five animals. After determination of the four control ventricular fibrillation thresholds, tocainide was administered over 90 minutes. For the first 45 minutes each animal received tocainide at a rate of 0.24 mg/kg per min. Ventricular fibrillation threshold was determined 15, 30 and 45 minutes after the onset of drug infusion. At the end of 45 minutes the rate of drug infusion was changed according to the change in ventricular fibrillation threshold from control value. If the increase in threshold was less than 50%, the infusion rate was doubled. If the threshold increased 50 to 200 percent above the control value, no change was made in the infusion rate. If the threshold increased by more than 200 percent, the infusion rate was halved. The new infusion rate was maintained for an additional 30 minutes, and ventricular fibrillation thresholds were measured at 15 and 30 minutes (60 and 75 minutes of drug administration). At the end of this 30 minute infusion the rate of infusion was again changed according to the criteria just described, and the new infusion rate was maintained for 15 minutes. The total amount of tocainide administered to these animals ranged from 18.9 to 38.5 mg/kg. These variable infusion rates were used to span a wide range of ventricular fibrillation thresholds and plasma

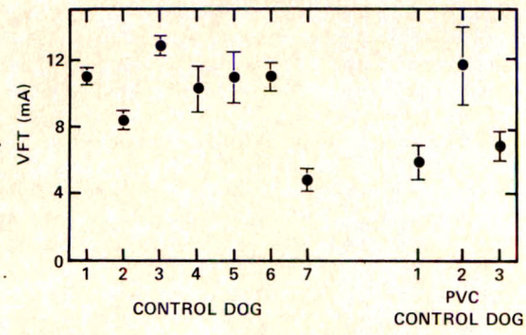

FIGURE 1. Control group. Average ventricular fibrillation threshold (VFT) for each of the control dogs. There were seven control dogs for threshold measured during paced supraventricular complexes **(left)** and three control dogs for threshold measured during induced premature ventricular complexes (PVC) **(right).** The values for each animal **(closed circles and bars)** represent the average (± standard deviation) ventricular fibrillation threshold measured at 15 minute intervals over 270 minutes. mA = milliampere.

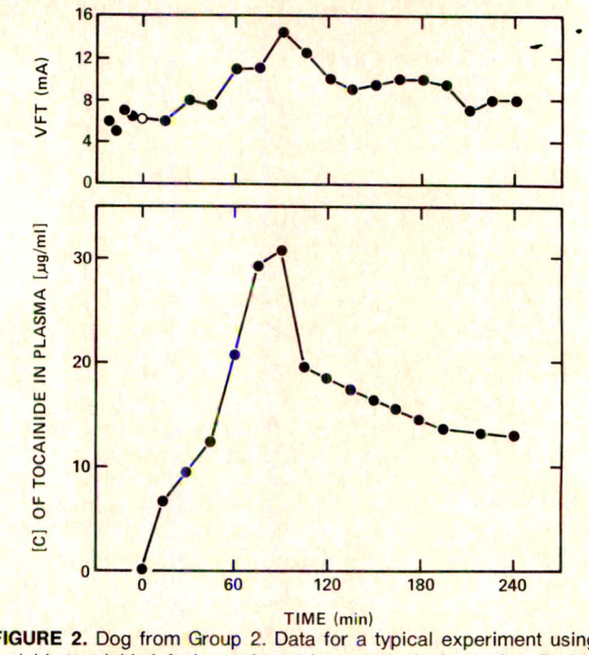

FIGURE 2. Dog from Group 2. Data for a typical experiment using variable tocainide infusion and paced supraventricular rhythm. During the 90 minute period of drug infusion, tocainide plasma concentration ([**C**]) increases to a peak of approximately 30 μg/ml **(lower graph).** Simultaneously the ventricular fibrillation threshold **(upper graph)** increases from a control value of 6 to a drug-induced value of 14 milliamperes (mA). Both tocainide plasma concentration and ventricular fibrillation threshold decrease after 90 minutes.

concentrations. After the 90 minute period of drug infusion, determinations of ventricular fibrillation threshold were continued at 15 minute intervals until the threshold returned to, or nearly to, the control value.

Group 3 (small dose constant tocainide infusion): Because the experiments in Group 2 produced maximal tocainide plasma concentrations much greater than those in patients treated with the drug, studies were carried out in four animals during paced supraventricular rhythm to evaluate the effect of lesser tocainide concentrations on ventricular fibrillation threshold. After the four control determinations of ventricular fibrillation threshold, these animals were given constant infusions of tocainide ranging from 0.15 to 0.175 mg/kg per min for 90 minutes. The total dose of tocainide administered to these animals ranged from 13.4 to 15.8 mg/kg. Both during and after drug infusion, ventricular fibrillation threshold was determined at 15 minute intervals.

Group 4 (variable lidocaine infusion). In this group, five animals were studied during paced supraventricular rhythm, using a variable infusion rate regimen similar to that used for the animals in group 2 receiving tocainide. Each animal received a 90 minute infusion of lidocaine. The initial infusion rate of 0.24 mg/kg per min was maintained for 45 minutes. At 45 and 75 minutes after the start of the infusion, the infusion rate was either maintained, doubled or halved, on the basis of change in ventricular fibrillation threshold as previously described for tocainide. The total dose of lidocaine administered to these animals ranged from 27.9 to 38.5 mg/kg. During and after drug administration, ventricular fibrillation threshold was determined at 15 minute intervals until threshold returned to, or nearly to, the control value.

Data analysis: For each animal the relation between normalized ventricular fibrillation threshold (ventricular fibrillation threshold divided by control ventricular fibrillation threshold for that animal) and the log plasma concentration was determined using a least squares linear regression. The correlation coefficient and significance of each linear regression line were determined using standard statistical techniques. To estimate the average increase in ventricular fibrillation threshold as a function of plasma concentration for the entire group, the slope and intercept of the regression lines from individual animals were averaged, and a concentration-response curve representative of the average animal was derived.

Results

Group 1 (control group): The seven control animals studied during paced supraventricular rhythm had an average ventricular fibrillation threshold of 9.9 milliamperes (range 4.9 to 12.8). For these seven animals the average standard deviation and the average coefficient of variation of ventricular fibrillation thresholds over 270 minutes were ±0.86 milliamperes (range 0.51 to 1.53) and 9.4 percent (range 5 to 14 percent), respectively. The three control animals studied during induced premature ventricular complexes had a mean ventricular fibrillation threshold of 8.3 milliamperes (range 5.9 to 12). Over the 270 minutes the standard deviation ranged from ±0.92 to ±2.3 milliamperes and the coefficients of variation were 14, 18, and 19 percent, respectively. The mean and standard deviation for each control animal are shown in Figure 1.

Group 2 (variable tocainide infusion): Figure 2 illustrates the data for a typical experiment during a variable tocainide infusion and paced supraventricular rhythm. During the infusion there is a rise in tocainide plasma concentrations from 0 to greater than 30 μg/ml. During this time the ventricular fibrillation threshold increases from 6 to 14 milliamperes. After the 90 minute infusion, the plasma concentration decreases rapidly, and the ventricular fibrillation threshold returns toward control values. Figure 3 shows the data for this animal, plotted as normalized ventricular fibrillation threshold versus log plasma concentration. This dog was typical of each of the 10 animals in that the onset of the in-

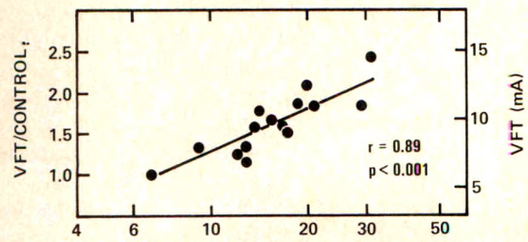

FIGURE 3. Same dog. Normalized ventricular fibrillation threshold (VFT/CONTROL) plotted against log tocainide plasma concentration. The values for correlation coefficient (r) and probability (p) are for the least squares regression line shown. mA = milliamperes.

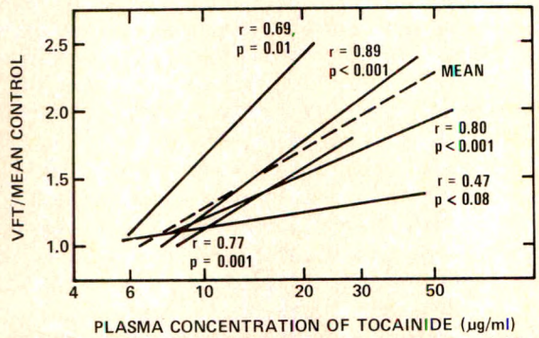

FIGURE 4. Group 2. Tocainide concentration-response relations for each of the five animals studied with variable tocainide infusion and ventricular fibrillation threshold (VFT) determined during paced supraventricular rhythm. Values for correlation coefficient (r) and probability (p) are given for each animal. The **dashed line** labeled MEAN represents the concentration-response relation for the average animal. There is little measurable effect on ventricular fibrillation threshold at tocainide concentrations of less than 6 μg/ml. Note the range of interanimal variation in sensitivity to tocainide. VFT/MEAN CONTROL = normalized ventricular fibrillation threshold.

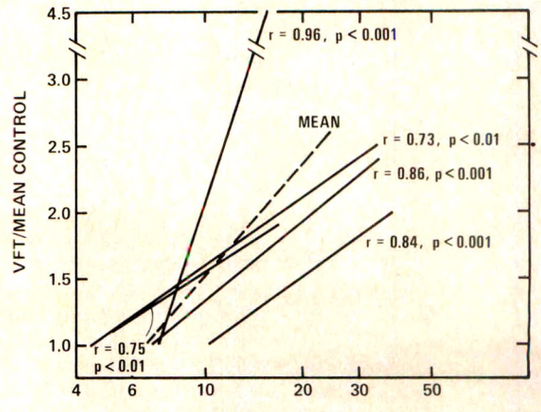

FIGURE 5. Group 2. Data as in Figure 4 except that in these five animals ventricular fibrillation threshold was measured during induced premature ventricular complexes.

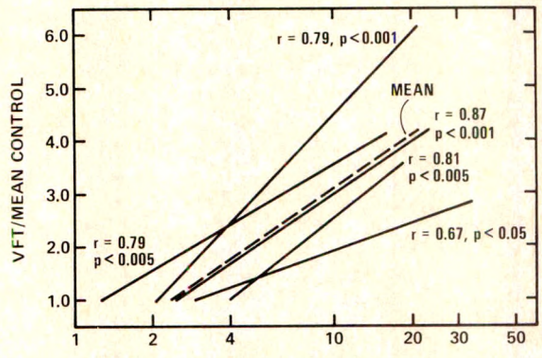

FIGURE 6. Group 4. Lidocaine concentration-response relations for each of the five animals studied during paced supraventricular rhythm. Values for correlation coefficient (r) and probability (p) are given for each animal. Note the range of interanimal variation in plasma concentration at which the onset of measurable effect is noted and the variation in sensitivity to lidocaine. The **dashed line** labeled MEAN represents concentration-response relation for the average animal. Abbreviations as in Figure 4.

crease in ventricular fibrillation threshold generally occurred at a tocainide plasma concentration of more than 6 to 10 μg/ml, and in the range studied beyond this there was a linear relation between increase in ventricular fibrillation threshold and log plasma tocainide concentrations.

The linear regression lines for each of the five animals studied during paced supraventricular rhythm are shown in Figure 4. The probability (P) value for the slope of each line is highly significant for four dogs (range <0.001 to <0.004) and of borderline significance for one dog (P <0.08). There is a wide range of sensitivity of the animals to tocainide, as evidenced by the interanimal variation of the slopes of the log concentration response curves. The concentration-response relation representing the average animal is also indicated in Figure 4. This average curve showed that at a plasma concentration of 10 μg/ml, tocainide increased the ventricular fibrillation threshold by 28 percent (range 14 to 67 percent), at 15 μg/ml by 53 percent (range 28 to 111 percent and at 20 μg/ml by 71 percent (range 37 to 143 percent).

The linear regression lines for each of the five animals studied during induced premature ventricular complexes are shown in Figure 5. The P value for the slope of each line is highly significant (range P <0.01 to P <0.001). For the supraventricular complexes there is little measurable effect at concentrations of 6 to 10 μg/ml and there is a wide range of interanimal variation of sensitivity to tocainide. The average increase in ventricular fibrillation threshold was 52 percent (range 0 to 120 percent) at 10 μg/ml, 102 percent (range 30 to 240 percent) at 15 μg/ml and 137 percent (range 53 to more than 300 percent) at 20 μg/ml. Although tocainide tended to increase the ventricular fibrillation threshold more during ventricular premature complexes than during paced supraventricular rhythm, the difference was not statistically significant.

Two animals in the tocainide series received a single intravenous injection of 125 mg of lidocaine at the end of the experiment after ventricular fibrillation threshold had returned to control value and the experiment was completed. Within 3 to 5 minutes of administration of the lidocaine bolus injection, the ventricular fibrillation threshold was again measured. In one dog the threshold increased to 123 percent above the mean control value compared with a peak effect of

54 percent for tocainide in the same animal. In the other, the threshold increased to 357 percent above the mean control value compared with a peak effect of 147 percent for tocainide in that animal. No simultaneous blood samples were obtained for determination of lidocaine concentration.

Group 3 (small dose constant tocainide infusion): The data for this group were treated in the same manner as the data for Group 2. The majority of plasma concentration measurements in this group were less than 10 μg/ml. When least squares linear regression lines were calculated for the normalized ventricular fibrillation threshold versus log plasma concentration plots, no significant correlation was found. These smaller dose infusion studies confirmed the finding of the larger dose variable rate infusion studies that tocainide has little effect on ventricular fibrillation threshold at plasma concentrations of less than 6 μg/ml. Although two animals demonstrated increases in ventricular fibrillation threshold at plasma concentrations greater than 6 μg/ml, there were in general too few data points in this concentration range to describe this relation quantitatively.

Group 4 (variable lidocaine infusion): Data for individual animals were obtained as for the animals receiving tocainide. Figure 6 shows the linear regression lines of normalized ventricular fibrillation threshold versus log plasma concentration for the five animals studied at variable infusion rates of lidocaine. The relation between the rise in ventricular fibrillation threshold and drug plasma concentration is significant in all animals ($P < 0.015$ to < 0.001). As with tocainide, there is a wide range of individual animal sensitivity to lidocaine. Also, as with tocainide, the ventricular fibrillation threshold continues to increase at increasing plasma concentrations within the range examined. The average response is also shown in Figure 6. At a lidocaine plasma concentration of 4 μg/ml, the average increase in ventricular fibrillation threshold was 77 percent (range 2 to 146 percent), at 6 μg/ml 136 percent (range 55 to 235 percent) and at 8 μg/ml 177 percent (range 76 to 299 percent).

Discussion

Effects of tocainide versus lidocaine on ventricular fibrillation threshold: This study evaluating the effects of tocainide and lidocaine on the ventricular fibrillation threshold provides concentration-response curves for each of these drugs over a wide range of ventricular fibrillation thresholds and plasma concentrations. Examination of the concentration-response relation for individual animals yields several important findings. For both tocainide and lidocaine, individual animals showed wide variability in the plasma concentrations at which the onset of measurable effect was observed. Thus, at any given small plasma concentration of these agents, some animals may have a considerable increase in the ventricular fibrillation threshold whereas others may have little or no increase. Additionally, there is a wide range in sensitivity of these animals to each of the drugs, as evidenced by the wide range of slopes of the plasma concentration-response relation. Thus, even at greater plasma concentrations, for any given drug plasma concentration one animal may have a much greater increase in ventricular fibrillation threshold than another animal. This variability of response prompted us to use the variable infusion rate regimen described in the Methods section. The use of a fixed infusion rate, rather than a regimen based on observed response, did not consistently provide a sufficient range of response. These observations of individual animal concentration-response curves for the relation between ventricular fibrillation threshold and plasma concentration correspond with our observations on the relation between reduction of premature ventricular complexes and plasma concentration of tocainide in man[4]; that is, there is a wide range of intersubject variability in these concentration-response relations.

Our findings of a concentration-dependent increase in ventricular fibrillation threshold with lidocaine confirm the previous work of Spear and Gerstenblith and their co-workers.[8,9] They examined this relation at lesser plasma concentrations of lidocaine but were unable to examine greater plasma concentrations because of adverse hemodynamic effects. In our study we continuously monitored arterial blood pressure and did not observe major hemodynamic embarrassment in any animal despite lidocaine plasma concentrations of up to 20 μg/ml in many animals. Our data therefore extend the observations of previous studies to greater lidocaine concentrations. Similarly, we investigated the effect of tocainide on ventricular fibrillation threshold at concentrations at and above those used clinically. For both drugs we continued to observe increases in ventricular fibrillation threshold at plasma concentrations greater than those used clinically.

Clinical implications: Our animal data suggest that there may be advantages in continuing drug administration beyond the point when ventricular ectopic complexes are suppressed or minimal or average "therapeutic" plasma concentrations are achieved. There is some clinical evidence to support the concept that greater lidocaine concentrations are more protective against ventricular fibrillation. Lie et al.[10] found that lidocaine was protective against ventricular fibrillation early after myocardial infarction but noted that several earlier investigations[11,12] had not found an effect of lidocaine on the occurrence of ventricular fibrillation. Although there are several possible explanations for this discrepancy, Lie et al.[10] offered as one explanation their use of a larger dose of lidocaine.

One must be extremely cautious in directly extrapolating the findings of our animal study to the clinical setting. The relation of ventricular fibrillation threshold to the spontaneous occurrence of ventricular fibrillation is unknown. Spontaneous ventricular fibrillation in man is frequently observed in patients with myocardial ischemia, and ischemia was not present in our animals. Finally, the direct extrapolation of plasma concentration-response data from one species to another may not be valid.

Comparison of the clinically tolerated ranges of plasma concentrations of lidocaine[13] and tocainide suggests that lidocaine is considerably more effective than tocainide in increasing ventricular fibrillation threshold. However, previous animal studies by Coltart et al.[14] showed that in the dog tocainide concentrations of 15 to 30 μg/ml are required for suppression of ventricular ectopic complexes. These plasma concentra-

tions are well above the 6 to 10 μg/ml range required for suppression of ventricular ectopy in man, suggesting a species difference in sensitivity to the electrophysiologic effects of tocainide.

Although there was a slight tendency for tocainide to provide greater increases in ventricular fibrillation threshold during premature ventricular complexes than during supraventricular complexes, this difference was not statistically significant. One possible explanation for this finding is related to the experimental design of our study. The premature ventricular complexes were induced by means of a left ventricular electrode, and ventricular fibrillation determinations were made using a right ventricular electrode site. Because premature ventricular complexes cause increased temporal dispersion over a relatively small anatomic area,[15] it is possible that we would have noted a greater effect of tocainide on ventricular fibrillation threshold determined during premature ventricular complexes had we used the same electrode for both introduction of premature complexes and determination of fibrillation threshold.

In summary, our study demonstrates that both tocainide and lidocaine significantly increased the ventricular fibrillation threshold in dogs. In individual animals there was a linear relation between increases in ventricular fibrillation threshold and plasma drug concentration. The response to both drugs ranged widely among individual animals. Although major increases in ventricular fibrillation threshold occurred only at tocainide plasma concentrations greater than those required for suppression of premature ventricular complexes in man, previous data on the plasma tocainide concentrations required to suppress ventricular ectopy suggest that this finding may be due in part to a species difference in sensitivity to tocainide.

References

1. **Winkle RA, Meffin PJ, Fitzgerald JW, et al:** Clinical efficacy and pharmacokinetics of a new orally effective antiarrhythmic, tocainide. Circulation 54:884–889, 1976
2. **Lalka D, Meyer MB, Duce BR, et al:** Kinetics of the oral antiarrhythmic lidocaine congener, tocainide. Clin Pharmacol Ther 19:757–766, 1976
3. **McDevitt DG, Nies AS, Wilkinson GR, et al:** Antiarrhythmic effects of a lidocaine congener, tocainide, 2-amino-2′, 6′-propionoxylidide, in man. Clin Pharmacol Ther 19:396–402, 1976
4. **Meffin PJ, Winkle RA, Blaschke TF, et al:** Response optimization of drug dosage: antiarrhythmic studies with tocainide. Clin Pharmacol Ther 22:42–57, 1977
5. **Moore EN, Spear JF:** Ventricular fibrillation threshold: its physiological and pharmacological importance. Arch Intern Med 135: 446–453, 1975
6. **Meffin PJ, Harapat SR, Harrison DC:** High pressure liquid chromatographic analysis of drugs in biological fluids. II. Determination of an antiarrhythmic drug, tocainide, as its dansyl derivative using a fluorescence detector. J Pharm Sci 66:583–586, 1977
7. **Benowitz NL, Rowland M:** Determination of lidocaine in blood and tissues. Anesthesiology 39:639–641, 1973
8. **Spear JF, Moore EN, Gerstenblith G:** Effect of lidocaine on the ventricular fibrillation threshold in the dog during acute ischemia and premature ventricular contractions. Circulation 46:65–73, 1972
9. **Gerstenblith G, Spear JF, Moore EN:** Quantitative study of the effect of lidocaine on the threshold for ventricular fibrillation in the dog. Am J Cardiol 30:242–247, 1972
10. **Lie KI, Wellens HJ, van Capelle FJ, et al:** Lidocaine in the prevention of primary ventricular fibrillation: a double-blind, randomized study of 212 consecutive patients. N Engl J Med 291: 1324–1326, 1974
11. **Darby S, Bennett MA, Cruickshank JC, et al:** Trial of combined intramuscular and intravenous lignocaine in prophylaxis of ventricular tachyarrhythmias. Lancet 1:817–819, 1972
12. **Church G, Biern R:** Prophylactic lidocaine in acute myocardial infarction (abstr). Circulation 40, 41:Suppl II:II-139, 1972
13. **Gianelly R, von der Groeben JO, Spivack AP, et al:** Effect of lidocaine on ventricular arrhythmias in patients with coronary heart disease. N Engl J Med 277:1215–1219, 1967
14. **Coltart DJ, Berndt TB, Kernoff R, et al:** Antiarrhythmic and circulatory effects of Astra W36095: a new lidocaine-like agent. Am J Cardiol 34:35–40, 1974
15. **Han J, Garcia de Jalon PD, Moe GK:** Fibrillation threshold of premature ventricular responses. Circ Res 18:18–25, 1966

Left Ventricular Function in Exercise-Induced Hypertrophy in Dogs

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Indexes of left ventricular function and diastolic compliance were studied in 10 awake exercise-trained greyhounds with left ventricular hypertrophy. Mean left ventricular to body weight ratio and mean myocardial cell diameter were significantly greater than in normal dogs (8.73 ± 2.7 [standard error of the mean] versus 4.63 ± 0.24 g/kg, $P < 0.01$; and 18.3 ± 0.67 versus 12.5 ± 0.71 μ, $P < 0.01$, respectively). In awake resting animals, 7 to 50 days after implantation of a high fidelity micromanometer and sonomicrometer crystals, left ventricular contractility indexes were similar to those measured previously in normal dogs (maximal derivative of left ventricular pressure [dP/dt] 3,800 ± 250 versus 3,810 ± 330 mm Hg/sec, difference not significant; and mean rate of circumferential fiber shortening 1.54 ± 0.12 versus 1.43 ± 0.12 sec^{-1}, difference not significant). During volume loading sufficient to produce a left ventricular end-diastolic pressure of 20 mm Hg, changes in contractility indexes were similar to those in normal dogs; however, heart rate increased significantly (74 percent, $P < 0.005$) in the trained greyhounds but not in normal dogs. Left ventricular diastolic stiffness did not differ from normal (51.6 ± 3.0 versus 45.9 ± 5.9 mm Hg/cm, $P < 0.01$). These findings suggest that left ventricular function in exercise-induced left ventricular hypertrophy is substantially normal.

Left ventricular hypertrophy resulting from chronic pressure overload has been associated with both normal[1,2] and reduced[3–6] indexes of myocardial contractility even in the absence of congestive heart failure. Meerson and Pshennikova[7] observed higher than normal values for peak left ventricular pressure and tension-time index in the isovolumically beating left ventricle of rabbits with myocardial hypertrophy due to pressure overload. However, these variables were less than normal when calculated per unit of left ventricular mass, indicating an apparent decrease in performance of the chronically pressure-loaded left ventricle. Similar findings of depressed function in pressure overload hypertrophy based on factors related to contractile element velocity have been reported in papillary muscles from hypertrophied right ventricles in cats[6] and in intact canine left ventricles.[4] As Simon et al.[5] have pointed out, some (but not all) of the conflicting results may be based on differences in experimental procedures and the indexes used to evaluate myocardial performance. On the other hand, ventricles with hypertrophy due to chronic volume overload have been reported to have normal or enhanced performance in animals without heart failure[8,9] and even in animals with severe congestive failure.[10]

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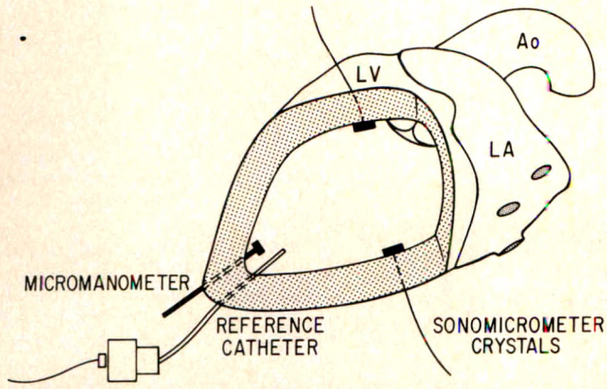

FIGURE 1. Schematic sectioned view of the left ventricular chamber showing the placement of instruments. A high fidelity micromanometer and a pressure reference catheter were introduced near the apex of the left ventricle (LV) and secured with purse-string sutures. The sonomicrometer crystals were introduced at the maximal left ventricular diameter and placed snug against the endocardium. While the crystals were being introduced, care was taken to avoid placing them on the papillary muscles. Crystal location was verified in each animal at postmortem examination. Ao = aorta; LA = left atrium.

At present there is little comparable information with regard to left ventricular hypertrophy produced by chronic severe exercise. Exercise-induced hypertrophy is generally considered benign, but the induction of the hypertrophied state through repetitive periods of strenuous exercise has at least some features of chronic pressure overload as well as of chronic volume overload. We therefore examined in the left ventricle of dogs with exercise-induced hypertrophy (1) the nature of changes, if any, in myocardial performance and contractility, and (2) changes in diastolic compliance because decreased left ventricular diastolic compliance has been reported in patients with aortic valve stenosis[11] and in dogs with chronic volume overload.[12] Studies of the isovolumic and ejection phases of contraction and diastolic compliance were carried out in conscious exercise-trained greyhounds previously fitted with instruments. The results were compared with those in normal dogs with similar instrumentation studied in our laboratory.[9,12,13] A preliminary report of this work has appeared elsewhere.[14]

Methods

Adult greyhounds (body weight 25 to 30 kg) were obtained after they had been culled from a 4 month race-training program or after the training program plus a racing career of 2 to 18 months' duration. The typical training program for racing greyhounds in the southwestern United States consists of daily sprint and endurance running lasting about 1 to 1 1/2 hours but, because the dogs were not obtained from a single trainer, training may not have been identical in every animal. In addition, the animals had undergone a variable (1 month or less) period of deconditioning before the study.

Operative procedure and instrumentation: Ten race-trained greyhounds were anesthetized with pentobarbital (30 mg/kg body weight) or thiopental (30 mg/kg), and a left thoracotomy was performed through the fifth intercostal space. The heart was cradled in the pericardium. A high fidelity micromanometer (Konigsberg Instruments, Pasadena, California, model P-20) and a polyvinyl catheter were introduced into the left ventricle by way of the apex and secured in place with purse-string sutures. Two 4.5 mm ultrasonic crystals[15] were implanted at the level of the left ventricular minor axis for measurement of instantaneous chamber diameter (Fig. 1). When it was certain that the signal from the transmitting piezoelectric crystal was being adequately received at the other crystal[16] and that both crystals were against the endocardial surface, the crystal lead wires were stitched in place to the epicardium. Crystal placement was verified at autopsy. The lead wires and catheters were brought out of the thorax in the sixth intercostal space and tunneled under the skin to the back of the neck. The thoracotomy was closed in the routine manner, and the animals were allowed to recuperate for 7 to 10 days before the first study. Both crystals were against the endocardial surface, the crystal lead wires were stitched to the epicardium and the pericardium was loosely reapproximated with two sutures.

Studies in the conscious animal: The greyhounds were trained to lie quietly on the table and were studied under resting conditions two to five times over a period of 3 to 6 weeks after the recovery period, and the data from each study were averaged. The lead wires for the ultrasonic crystals, the left ventricular high fidelity manometer lead cable and the left ventricular catheter were exteriorized and connected to the recording equipment.

The left ventricular catheter was connected to a Statham P23Db transducer and served as a pressure reference for calibration of the high fidelity manometer. Left ventricular pressure and a high gain representation of the 0 to 40 mm Hg pressure range of the left ventricular pressure (for determining left ventricular end-diastolic pressure) were recorded from both the catheter system and the high fidelity manometer. The time derivative of left ventricular pressure (dP/dt) was recorded from the high fidelity manometer only. We also recorded the instantaneous left ventricular diameter from the ultrasonic crystals and a limb lead of the electrocardiogram. All signals were displayed on an eight channel Clevite-Brush recorder at paper speeds of 100 or 200 mm/sec. Data from five to six beats (one respiratory cycle) were averaged.

After these variables were recorded under resting conditions, a volume load of up to 700 ml of 6 percent dextran in normal saline solution was rapidly infused intravenously through a percutaneous cannula. In most cases, this volume load was sufficient to increase left ventricular end-diastolic pressure from a resting value of 7 to 10 mm Hg to a value greater than 20 mm Hg.

Morphologic studies: Each animal was then anesthetized and the heart fixed in situ by retrograde infusion of 2.5 percent glutaraldehyde into the aortic root while left ventricular pressure was maintained at the animal's normal level of end-diastolic pressure using a reservoir connected to a cannula introduced into the left ventricle through the left atrial appendage. Histologic sections were taken parallel to the long axis of the heart and stained with hematoxylin-eosin. Myocardial cell diameter was measured only in cells that were sectioned perpendicular to their long axis and that had a centrally located cell nucleus. The requirement that the section be perpendicular to the long axis of the cell was insured by restricting the observation to areas very close to midway between endocardium and epicardium where fibers are circumferentially oriented. Measurements were obtained in 50

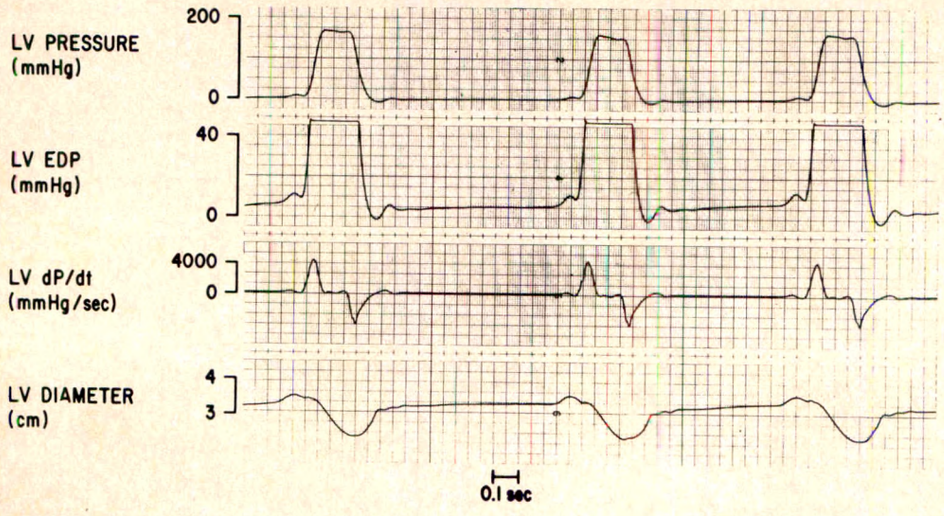

FIGURE 2. Representative tracing from an awake resting greyhound. The left ventricular (LV) pressure **(top tracing)** was obtained with the implanted high fidelity micromanometer. The amplified left ventricular pressure **(second tracing)** was recorded for ease in determining left ventricular end-diastolic pressure (EDP). The **third tracing** (dP/dt) was obtained by differentiating the left ventricular pressure signal through a Biotronix model BL 620 differentiating circuit. The diameter of the left ventricular chamber, obtained with the sonomicrometer crystals, is shown at **bottom.**

such cells in each heart. Normal myocardial cell diameters were obtained in six hearts fixed in an identical fashion.

Results

Left ventricular hypertrophy: Both left ventricular to body weight ratio (8.3 ± 2.7 g/kg [mean ± standard error of the mean]) and myocardial cell diameter (18.3 ± 0.67μ) were significantly larger than in (1) normal dogs of the same body weight range (4.63 ± 0.24 g/kg and 12.5 ± 0.7μ, respectively; $P < 0.01$) and (2) two greyhounds that had not undergone the rigorous training program (average 6.8 g/kg and 14.1 μ, respectively).[14,17] These data suggest that although there may be a significant degree of hypertrophy in greyhounds due to genetic factors alone, trained greyhounds had even more extensive left ventricular hypertrophy.

Hemodynamic and left ventricular dimensional measurements at rest: Figure 2 shows a representative tracing obtained in the resting state in an awake race-trained greyhound. Hemodynamic and left ventricular dimensional data from studies of isovolumic and ejection phase indexes of contractility in 10 awake dogs are shown in Table I. The data from two dogs in which only ejection phase indexes were measured and from one dog in which only isovolumic phase indexes were measured are included. Peak left ventricular systolic pressure, left ventricular end-diastolic pressure and peak left ventricular dP/dt averaged 143, 8.6 and 3,800 mm Hg/sec, respectively, and were not significantly different from values obtained in normal dogs.[13] Heart rate averaged 78 min^{-1} and was significantly lower than that of normal animals studied in the same laboratory (113 min^{-1})

TABLE I

Hemodynamic Variables and Measures of Contractility in Awake Racing Greyhounds

Dog no.	Heart Rate (min^{-1})	LVSP (mm Hg)	LVEDP (mm Hg)	End-Diastolic Diameter (cm)	Change in LV Diameter (%)	Isovolumic Phase Contractility (mm Hg/sec) Max dP/dt	Isovolumic Phase Contractility (mm Hg/sec) dP/dt/DP40	Ejection Phase Contractility (fraction of initial length/sec) Mean VCF	Ejection Phase Contractility (fraction of initial length/sec) Max VCF
1	84	137	6	4.7	20.0	. . .	. . .	1.18	1.60
2	49	137	5.5	4.4	24.6	. . .	. . .	1.28	1.68
3	70	147	11	4.6	23.8	4500	99	1.36	1.89
4	101	152	8.5	4.6	18.8	4300	84	1.38	1.68
5	48	150	5.5	. . .	. . .	2900	60	. . .	. . .
6	87	133	6.2	5.1	20.2	3200	71	1.39	1.83
7	120	155	11	4.9	26.3	5000	103	2.05	2.64
8	70	137	9	3.6	33.6	3100	68	2.27	2.40
9	78	142	15	4.5	20.7	3400	81	1.40	1.83
10	68	141	8.5	4.6	25.4	4300	84	1.55	2.26
Mean	78	143	8.6	4.55	23.7	3800	81	1.54	1.98
±SEM	7.2	2.2	1.0	0.17	1.6	250	5.4	0.12	0.12

dP/dt/DP40 = time derivative of left ventricular pressure when developed pressure equals 40 mm Hg divided by the developed left ventricular pressure (that is, 40 mm Hg); LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular systolic pressure; max dP/dt = maximal value of time derivative of left ventricular pressure; Max VCF = maximal velocity of circumferential fiber shortening = maximal time derivative of left ventricular diameter during ejection divided by end-diastolic diameter; Mean VCF = mean velocity of circumferential fiber shortening (end-diastolic diameter − end-systolic diameter)/end-diastolic diameter/ejection time; SEM = standard error of the mean.

TABLE II

Comparison of the Isovolumic Phase and Ejection Phase Indexes of Left Ventricular Contractility in Racing Greyhounds and Normal Dogs in the Resting State

	Isovolumic Phase (mm Hg/sec)		Ejection Phase (fraction of initial length/sec)	
	Max dP/dt	dP/dt/DP40	Mean VCF	Max VCF
Present study (racing greyhounds)	3800 ± 250 (no. = 8)	81 ± 5.4 (no. = 8)	1.54 ± 0.12 (no. = 9)	1.98 ± 0.12 (no. = 9)
Previous study (normal dogs)	3810 ± 330* (no. = 6)	82.2 ± 9.7* (no. = 6)	1.43 ± 0.12† (no. = 5)	. . .

* Data from Mahler et al.[13]
† Data from Ross and McCullagh.[9]
no. = number of dogs; other abbreviations as in Table I.

under identical conditions.[13] In the resting state the trained greyhounds tended to have a marked sinus arrhythmia associated with respiration.

Table II compares the mean values of left ventricular and ejection phase contractility indexes observed in the trained greyhounds with those observed in normal dogs in our laboratory.[9,13] Peak left ventricular dP/dt averaged 3,800 mm Hg/sec, and the ratio of dP/dt to developed pressure at 40 mm Hg averaged 81 sec^{-1}. Mean and peak circumferential fiber shortening rate[18] averaged 1.54 and 1.98 cm/sec, respectively.

Effects of volume loading: Figure 3 shows the average values of hemodynamic measurements and indexes of contractility at five points during a rapid infusion of dextran. The volume load was sufficient to raise left ventricular end-diastolic pressure from an operating level of 8.6 ± 0.6 to 21.9 ± 0.6 mm Hg. During the volume infusion heart rate was uncontrolled in these conscious animals and increased from 79 ± 9.6 to 138 ± 10.5 min^{-1} ($P < 0.01$). Left ventricular systolic pressure increased 6 percent over its control value of 156 ± 5.5 mm Hg (difference not significant), and end-diastolic diameter increased from 4.55 ± 0.30 to 4.77 ± 0.29 cm ($P < 0.001$ by paired t test). Neither stroke excursion nor mean rate of circumferential fiber shortening changed significantly from their respective control

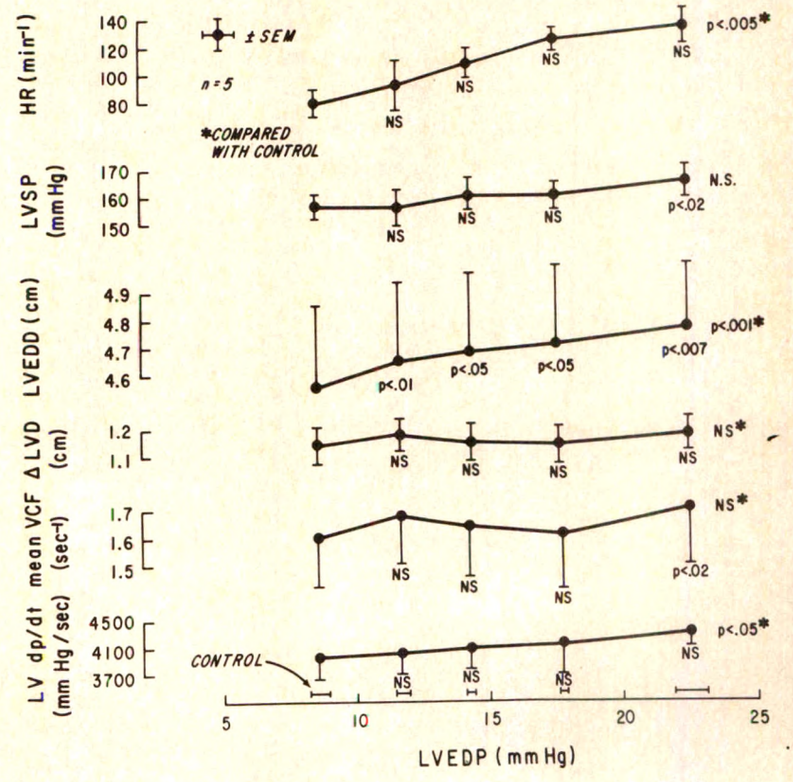

FIGURE 3. Left ventricular hemodynamic indexes measured during a volume load of 6 percent dextran in saline solution in five awake trained greyhounds. **Solid circles** represent mean values; **bars** represent standard error of the mean (SEM). The values below the solid circles represent significance of differences between the indicated mean value and the mean value at the next lower level of left ventricular end-diastolic pressure by a two-tailed t test for paired data. ΔLVD = change of left ventricular diameter during systole; HR = heart rate; LV dp/dt = maximal time derivative of left ventricular pressure; LVEDD and LVEDP = left ventricular end-diastolic diameter and pressure, respectively; LVSP = peak left ventricular systolic pressure; n = number of dogs; NS = not significant; p = probability; VCF = velocity of circumferential fiber shortening during ejection phase of systole.

TABLE III

Effect of Volume Loading on Indexes of Contractility in Racing Greyhounds and Normal Dogs

	Heart Rate (min^{-1})		LVSP (mm Hg)		LVEDP (mm Hg)		Isovolumic Indexes (mm Hg/sec) Max dP/dt		dP/dt/DP40		Ejection Indexes (fraction of initial length/sec) Mean VCF		Max VCF	
	C	I	C	I	C	I	C	I	C	I	C	I	C	I
Racing Greyhounds (no. = 5)														
Mean	79	138	156	165	8.6	21.9	3942	4346	87	90	1.60	1.70	2.11	2.16
SEM	9.6	10.5	5	6	0.6	0.6	267	257	6	4	0.18	0.16	0.18	0.18
P	0.005		NS		0.001		0.05		NS		NS		NS	
Normal dogs* (no. = 6)														
Mean	113	125	143	163	9.7	20.5	3890	4320	90	97.9	2.30	2.11	3.05	2.93
SEM	8	12	4	5	1.1	1.3	400	360	9.9	9.1	0.24	0.20	0.25	0.27
P	NS		0.001		0.001		0.05		0.05		NS		NS	

* Data from previous study.[13]

The absolute values of mean and maximal VCF observed in the previous study in normal dogs[13] were systematically higher than those in this study but did not change with volume loading. At the more apical location of the ultrasonic crystals used in the former study the percent shortening of circumferential fibers is greater.[18] C = control; I = intervention; volume load of 6 percent dextran; NS = not significant; *P* = significance by two-tailed *t* test for paired data. Other abbreviations as in Table I.

values of 1.14 ± 0.07 cm and 1.60 ± 0.18 sec^{-1}. During the volume load maximal dP/dt increased by 10 percent ($P < 0.05$) over the control value of 3,940 ± 270 mm Hg/sec. Table III summarizes the extent to which contractility indexes changed during volume loading in this study and in the previous study of normal dogs.[13]

Diastolic stiffness of the left ventricular chamber was assessed by plotting the relation between end-diastolic pressure and end-diastolic diameter during a volume load of dextran (Fig. 4). Although many of the individual sets of data points could be fitted to an exponential function, as suggested by Noble et al.,[19] to permit comparison among dogs in this study and with previously studied normal dogs, we used the simple linear least-squares fitted lines shown. The mean slope of the regression lines for the five dogs was 51.6 ± 3.0 mm Hg/cm.

Discussion

Significant left ventricular hypertrophy in the race-trained greyhounds was documented in our study by the increased left ventricular to body weight ratio and increased myocardial cell diameter compared with values in hearts of normal dogs. We have shown in another study (preliminary results have been reported[17]) that left ventricular chamber diameter was approximately 30 percent greater in hearts of trained greyhounds than in normal dogs of similar body weight. Left ventricular free wall thickness was also 50 percent greater in the trained greyhounds.

Comparison with previous studies in normal dogs: Results of our study suggest that neither isovolumic phase nor ejection phase indexes of contractility[20] are altered in the hypertrophied greyhound heart under resting conditions. The indexes of left ventricular contracility determined from high fidelity pressure manometry data (for example, dP/dt at a developed pressure of 40 mm Hg) were remarkably similar to those found by Mahler et al.[13] in a previous study of normal dogs using identical instrumentation. The mean velocity of circumferential fiber shortening, determined from left ventricular chamber diameter data (1.54 ± 0.12

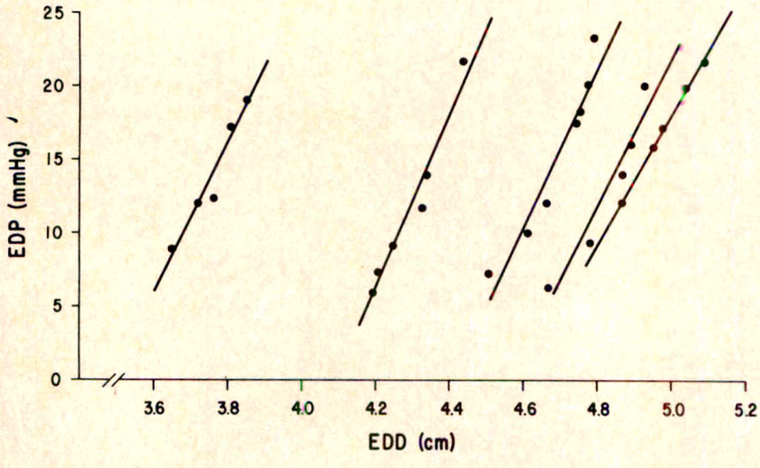

FIGURE 4. Relation of left ventricular end-diastolic pressure (EDP) and end-diastolic diameter (EDD) during volume loading in five awake trained greyhounds. The **lines** represent the best (least squares) linear fit of the data points. The left ventricular diastolic stiffness coefficients (the slope of the fitted lines) were, from left to right, 51.5, 59.1, 53.8, 49.9 and 43.9 mm Hg/cm (mean 51.6 ± 3.0). This value was not significantly different from the value of 45.9 ± 5.9 mm Hg/cm previously observed in normal dogs in our laboratory.[12]

sec^{-1}) was also not significantly different in the greyhounds than in normal dogs studied by Ross and McCullagh[9] (1.43 ± 0.12 sec^{-1}). Their technique for measuring for left ventricular chamber diameter (cineangiographic measurement of subendocardially implanted lead markers), differed from ours, but they obtained their data from a location at or near the maximal left ventricular diameter as in our study. Mahler et al.,[13] using the same ultrasonic instrumentation we used, obtained higher values for mean and maximal circumferential fiber shortening rate (2.13 ± 0.27 sec^{-1} and 2.72 ± 0.26 sec^{-1}, respectively, in six experiments). Measurements were obtained at a more apical location than in our study. LeWinter et al.[21] recently showed that the extent of circumferential shortening, as a fraction of initial length, is almost twice as great near the apex of the heart as at the mid or basal portion of the left ventricle, and this may account for the apparent difference between the mean and maximal values for circumferential fiber shortening rate observed by Mahler et al. and by us.

Under the stress of a volume load of dextran, the hypertrophied greyhound heart showed essentially the same response with regard to ejection phase and isovolumic phase contractility indexes as the heart of normal dogs in a previous study.[13] With volume load, there was no significant change in mean velocity of circumferential fiber shortening in either group, whereas maximal dP/dt increased about 10 percent in both groups. The pronounced increase in heart rate of 75 percent above resting levels seen during volume loading was perhaps the most striking hemodynamic indication of the effects of race conditioning in the greyhounds. No comparable increase in heart rate was observed in normal animals after volume loading.[13]

The left ventricular diastolic stiffness measured from the slope of the curve of end-diastolic pressure and diastolic diameter was 51.6 ± 3.0 mm Hg/cm in our study; this value is similar to the value of 45.9 ± 5.9 mm Hg/cm observed in normal dogs in our laboratory.[12] The diastolic stiffness of the left ventricle in the greyhounds was not different from that of normal dogs despite the large increase in myocardial mass and myocardial wall thickness. This is perhaps explained by the larger left ventricular chamber dimension in the hypertrophied greyhound heart. The increase in mean wall tension due to the larger minor axis dimension apparently compensates for the increase in wall thickness so that wall stress (wall tension divided by wall thickness) may not differ significantly from that in normal dogs, thus yielding a normal left ventricular diastolic stiffness. The finding of normal left ventricular diastolic stiffness suggests that the myocardium with exercise-induced hypertrophy should be capable of adjusting cardiac output by means of the Frank-Starling mechanism in a normal fashion. However, during volume loading it was quite evident that conditioned greyhounds had a pronounced tendency at least initially, to increase cardiac output, as a result of increasing heart rate; this "Bainbridge" type of reflex is not evident under similar conditions in untrained dogs.[13]

Clinical implications: In man, training and the repetitive stress of exercise produce a variety of cardiovascular changes that have been called the "athletic heart syndrome."[21–25] The enlarged heart and gallop rhythm have led to the suggestion that the athlete's heart is in some sense diseased. A recent study by Roeske et al.,[26] using various noninvasive techniques including echocardiography, provides evidence that the rate of circumferential fiber shortening and ejection fraction do not differ in highly trained athletes and normal subjects. Their study and our study in dogs support the view that "physiologic hypertrophy" represents a useful adaptation to repetitive strenuous exercise.[27] Moreover, because the animals in our study were no longer in the training program, the changes represent those of exercise-induced hypertrophy and do not necessarily represent those of conditioning as such.

Our study demonstrates that left ventricular contractility during the isovolumic (maximal dP/dt) and ejection phases (rate of circumferential fiber shortening) of contraction is within normal limits in the trained greyhound at rest and under the stress of volume load. Because, in addition, the fractional change of diameter during systole (ejection fraction) and left ventricular diastolic compliance do not differ significantly from those of awake untrained animals, it appears that exercise-induced hypertrophy is a physiologic adaptation and can be considered a variant of normal.

References

1. **Malik AB, Abe T, O'Kane H, et al:** Cardiac function, coronary flow and oxygen consumption in stable left ventricular hypertrophy. Am J Physiol 225:186–191, 1973
2. **Sandler H, Dodge HT:** Left ventricular tension and stress in man. Circ Res 13:91–104, 1963
3. **Graham TP Jr, Jarmakani JM, Canent RV, et al:** Evaluation of left ventricular contractile state in childhood. Circulation 44:1043–1052, 1971
4. **Krayenbuhl HP, Pierce EC II, Agishi T:** Left ventricular dynamics in the dog under chronic pressure load from coarctation of the aorta. Arch Kreislaufforschung 56:1–25, 1968
5. **Simon H, Krayenbuhl HP, Rutishauser W, et al:** The contractile state of the hypertrophied left ventricular myocardium in aortic stenosis. Am Heart J 79:587–602, 1970
6. **Spanza JF Jr, Buccino RA, Sonnenblick EH, et al:** Contractile state of cardiac muscle obtained from cats with experimentally produced ventricular hypertrophy in heart failure. Circ Res 21:341–354, 1967
7. **Meerson FZ, Pshennikova MG:** Effect of myocardial hypertrophy on cardiac contractility. Fed Proc (Trans Suppl) 24:957–959, 1965
8. **Cooper G IV, Puga FJ, Zujko KJ, et al:** Normal myocardial function and energetics in volume-overloaded hypertrophy in the cat. Circ Res 32:140–148, 1973
9. **Ross J Jr, McCullagh WH:** The nature of enhanced performance of the dilated left ventricle during chronic volume overloading. Circ Res 30:549–556, 1972
10. **Taylor RR, Covell JW, Ross J Jr:** Left ventricular function in ex-

perimental aorta-caval fistula with circulatory congestion and fluid retention. J Clin Invest 47:1333–1342, 1968
11. **Gaasch WH, Battle WE, Oboler AA, et al:** Left ventricular stress and compliance in man. Circulation 45:746–762, 1972
12. **McCullagh WH, Covell JW, Ross J Jr:** Left ventricular dilatation and diastolic compliance changes during chronic volume overloading. Circulation 45:943–951, 1972
13. **Mahler F, Ross J Jr, O'Rourke RA, et al:** Effects of preload, afterload and inotropic state on ejection and isovolumic phase measures of contractility in conscious dogs. Am J Cardiol 35: 626–634, 1975
14. **Carew TE, Dennis CA, Covell JW:** Left ventricular function in exercise-induced hypertrophy (abstr). Fed Proc 33:380, 1974
15. **Stegall HF, Kardon MB, Stone HL, et al:** A portable, simple sonomicrometer. J Appl Physiol 23:289–293, 1967
16. **Kirkpatrick SW, Covell JW, Friedman WF:** A new technique for the continuous assessment of fetal and neonatal cardiac performance. Am J Obstet Gynecol 116:963–972, 1973
17. **Carew TE, Birkett IM, Joseph MG, et al:** Myocardial fiber angle distribution in chronic exercise hypertrophy and chronic cardiac dilatation in the dog (abstr). Fed Proc 32:433, 1973
18. **Karliner JS, Gault JH, Eckberg D, et al:** Mean velocity of fiber shortening: simplified measure of left ventricular myocardial contractility. Circulation 44:323–333, 1971
19. **Noble MIM, Milne ENC, Goerke RJ, et al:** Left ventricular filling and diastolic pressure-volume relations in the conscious dog. Circ Res 24:269–283, 1969
20. **Barach JH:** Physiological and pathological effects of severe exertion (the marathon race) on the circulatory and renal systems. Arch Intern Med 5:382–405, 1910
21. **LeWinter MM, Kent RS, Kroener JM, et al:** Regional differences in myocardial performance in the left ventricle of the dog. Circ Res 37:191–199, 1975
22. **Bechner GL, Winson T:** Cardiovascular adaptations to prolonged physical effort. Circulation 9:835–846, 1954
23. **Bromwell C, Ellis R:** Some observations on the circulatory mechanism in marathon runners. Q J Med 24:329–346, 1931
24. **Gott PH, Roselle HA, Crampton RS:** The athletic heart syndrome. Arch Intern Med 122:340–344, 1968
25. **Lichtman J, O'Rourke RA, Klein A, et al:** Electrocardiogram of the athlete. Arch Intern Med 132:763–770, 1973
26. **Roeske WR, O'Rourke RA, Klein A, et al:** Noninvasive evaluation of ventricular hypertrophy in professional athletes. Circulation 53:286–292, 1976
27. **Grande F, Taylor HL:** Adaptive changes in the heart, vessels, and patterns of control under chronically high loads. In, Handbook of Physiology, Vol 3, Sect 2 (Circulation) (Hamilton WF, Dow P, ed). Washington, DC, American Physiological Society, 1965, p 2615–2677

Problems in Ultrasonic Estimates of Septal Thickness

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Problems related to cardiac anatomy and ultrasonic instrumentation affect the accuracy of echographic identification of endocardial echoes. A cadaver model and 13 patients were studied, with direct identification or with the aid of echographic contrast techniques, to identify accurately the endocardial echo. The study showed that (1) echographic contrast agents delineate an endocardial echo in the central portion of the ultransonic beam; (2) a specular reflector exists within the right ventricular cavity; (3) specular reflectors within the septum may give the false appearance of border-forming echoes; (4) septal thickness varies by 1 to 5 mm after the endocardial echo has been identified by the contrast agent; and (5) spurious echoes, related to a wide beam angle, can be confused with the endocardial echo. In light of these problems, three criteria were utilized for endocardial echo identification: the prominent notch in the left septal echo, the specular quality of the right septal echo, and the association of multiple myocardial echoes moving in parallel. With these criteria, the endocardial echoes in 11 of the 13 patients could be accurately identified without the use of a contrast agent. The identification of these problems should provide helpful guidelines in developing more accurate and reproducible criteria for septal thickness measurements.

Previous investigators[1–3] have recognized several potential problems that interfere with the accuracy and reproducibility of echocardiographic measurements of the ventricular septum. To improve the reproducibility of these measurements, it has been proposed that a standardized beam angle be selected.[1,4] Although this guideline significantly decreases the variation in measurements of septal thickness, the physician evaluating echograms needs to be aware of other problems that may interfere with accurate assessment or produce variation in the estimation of septal thickness. Accurate assessment requires that the physician be able to distinguish endocardial echoes from spurious echoes related to a divergent ultrasonic beam and from specular (mirror-like) reflectors within the ventricular cavities or the interventricular septum. Variation in estimates of septal thickness may occur depending on the angle at which the beam crosses the septum or anatomic variation in septal thickness, or both. Although these problems are frequently mentioned, they have not been studied with methods that allow accurate endocardial identification. To identify these problems, we used a cadaver model and an echographic contrast agent that would enable us to delineate septal borders.

The purpose of the study was fourfold: (1) to document the existence of spurious echoes, related to beam width, that might lead to misidentification of the endocardial echo; (2) to show that anatomic variations in septal thickness can occur despite the use of standardized guidelines; (3) to demonstrate that intraseptal and intraventricular specular reflectors do exist; and (4) to evaluate criteria for identifying endocardial echoes after consideration of these problems.

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Methods

The investigation included two methods: (1) echocardiographic recordings from a cadaver model; and (2) echographic contrast studies in 13 patients. The cadaver was chosen in preference to an animal model because it allows precise identification of cardiac structures and permits removal of tissues to identify the origin of specific echoes. The cadaver also served as a model for studying an echographic contrast agent. In the cadaver model we studied the existence of spurious echoes, recorded echographic evidence of variations in septal thickness and evaluated the properties of sound reflection from a contrast agent. To determine if these observations apply to patients, we utilized an echographic contrast agent to identify the endocardial surface. This method has been established as the most accurate technique for identifying cardiac structures in a clinical investigation.

The study was conducted using a Unirad Sonograf D instrument. All recordings were made by one of two persons, using a 2.25 megahertz, 7.5 cm focused transducer 13 mm in diameter, and a 1856 Honeywell recorder.

Cadaver Study

The specimen was prepared for study in the following manner: A freshly embalmed cadaver was frozen and the tissue fixed in order to minimize anatomic distortion. Serial sagittal sections about 3 cm thick were cut through the chest wall. The section chosen for study was just medial to the junction of the anterior left ventricular wall and the ventricular septum. This section approximates the area of the ventricle traversed by the ultrasonic beam in standard echographic recordings. The chest wall was removed so that the cardiac structures could be recorded at a gain setting comparable with that used in the clinical study.

The following methods were utilized for ultrasonic examination: The specimen was immersed in a water bath. To simulate a clinical study, the transducer was placed about 4 cm from the septum at an angle that would allow the ultrasonic beam to pass through the left ventricular cavity at the level of the chordal attachment to the mitral valve leaflets.

The initial cadaver study evaluated the use of an echographic contrast agent to determine if this technique would identify as endocardial borders echoes that were in the central or peripheral portion of the beam. We injected saline solution through an 18 gauge needle as the contrast agent. Initially, the needle was placed in a perpendicular position adjacent to the septal wall at a site within the central portion of the beam. The needle was then moved along both septal walls until it was barely visible in the periphery of the beam (Fig. 1). As the needle was moved to the periphery, it appeared to be within the central beam but further from the transducer. The echographic contrast agent was injected into the left and right ventricular cavities to evaluate the relation between the needle echo in the central and peripheral beam locations and the echo identified as endocardial with the echographic contrast injection. There was some conjecture as to why echoes at the periphery of the beam appeared as distinct lines rather than as a continuous blend of echoes from a series of off-axis sources. We believe that this appearance can best be explained by the irregularity of the septal surface, which does not provide an even surface for reflection.

To identify an intraseptal specular reflector, and to differentiate it from an off-axis endocardial echo, we identified a penetrating branch of the left anterior descending coronary artery as a potential reflector. Once an echo was identified in the same location as the vessel, we carefully excised the vessel leaving the endocardial surfaces intact so that the sources of off-axis echoes would not be disturbed. Echograms were recorded before and after the vessel was removed to document the origin of the specific set of echoes located in the same position as the artery.

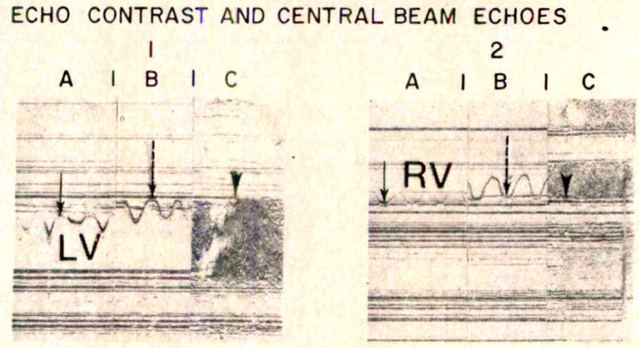

FIGURE 1. Echographic contrast and central beam echoes. The two series of echograms (1 and 2), show **(A)** the needle echoes at the periphery of the beam **(solid arrows), (B)** the needle echo in the center of the beam **(dashed arrows)** and **(C)** the echographic contrast injections. In series 1, the echographic contrast agent is injected into the left ventricle (LV) and in series 2 into the right ventricle (RV). In both series, the contrast agent delineates septal borders **(arrowheads)** approximating the border within the central beam **(dashed arrow)** rather than the periphery. The needle echo can be identified by its motion.

Echographic Contrast Studies in Patients

Echographic contrast studies were performed in 13 patients; 7 of these studies were used to demonstrate the principles outlined in this investigation. Each patient was selected after signing an informed consent form approved by the Hospital Research Committee. The study was performed in a cardiac catheterization laboratory as part of a routine catheterization. Indocyanine green was used as the contrast agent. Each study was made with the transducer placed along the left sternal border in either the third or the fourth intercostal space. The patient was lying in a right anterior oblique position. The intercostal space used was selected because it permitted the mitral valve to be recorded without tilting the transducer in a superior or inferior direction (mid transducer position).[4] This position was used for each recording unless otherwise indicated. Once the mid position intercostal space was determined, several recordings were made at different transducer positions but within the same interspace, and any changes in the echogram were noted. Deliberate attempts were made to reproduce the findings observed in the cadaver study. The beam angle that crossed the junction of the tips of the mitral leaflets with the chordae tendineae was selected for each septal echographic recording.

The echographic contrast agent was injected through a catheter in both the left and the right ventricles. The right ventricular injections were made using a power injector. The initial injection, of 10 cc of saline solution and 1 cc of indocyanine green, was made at a speed of 15 cc/sec. The speed was gradually increased, at increments of 2.5 cc/sec, until the contrast agent delineated a specific echo or abruptly stopped at an area that could be identified with a distinct echo at a selected beam angle. The echograms that best demonstrated the specific principle were chosen for illustration. Echographic contrast studies that showed reverberating contrast echoes throughout the entire thickness of the septum were excluded. The power injector allowed us to titrate the injection carefully to achieve an echogram that delineated a specific echo as a wall

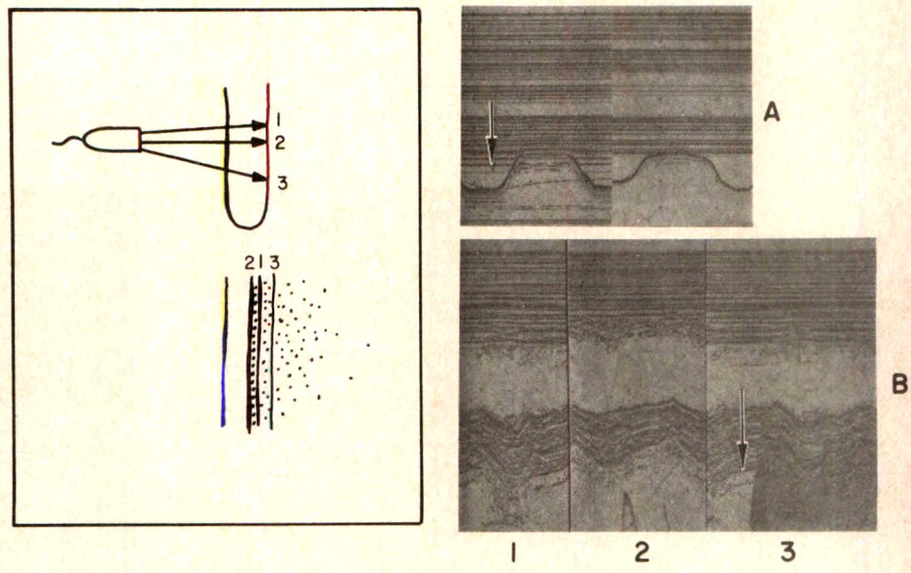

FIGURE 2. Off-axis extraseptal echoes. **A,** cadaver study; **B,** patient study. The drawing **(left)** illustrates off-axis echoes from a widened beam. The central endocardial echoes are identified by the moving reflector **(A)** or echographic contrast agent **(B)**. The **arrows** indicate off-axis echoes within the ventricular cavity in both studies. The middle recording (2) in **B** shows a more distinct central endocardial echo after adjustment of the beam angle.

border without producing reverberating echoes within the septal surface. The left ventricular injection was made by hand because reverberating echoes within the septal surface were not a problem.

The pictures chosen for illustration were often made several beats after the echographic contrast injection because premature beats were encountered with the injection. In 7 of the 13 patients studied, more than one measurement was obtained with the contrast agent. With each measurement, we recorded both the distance of the septum and the pericardial echo from the transducer. We assumed that the contrast agent would delineate echoes within the central portion of the beam as the endocardial echo. If there was a difference in septal measurement and this difference was associated with a change in the distance of the septum or pericardial echo from the transducer, we assumed that this variation was related to a change in the angle at which the beam crossed the septum or to an anatomic variation in septal thickness.

Sound Reflection Principles

In analyzing our results, we considered the problem of beam angle focus. The ultrasonic beam cannot be accurately focused and spreads out over a finite angle. This explains why off-axis echoes occur. The finite beam width creates a potential problem in using echographic contrast agents to delineate cardiac borders. If echoes from the contrast injection are reflected from a wide area of the beam, problems in identification of the anterior heart border will exist. Echoes reflected from the periphery of the beam will appear to be within the central beam but behind their actual location. Reflections from echographic contrast medium in the beam periphery would delineate echoes within the septal substance as the anterior septal border if they reached the transducer.

Definition of Terms

1. *Central beam endocardial echo:* the echo contiguous with the echographic contrast agent that fills a cardiac chamber.
2. *Endocardial dropout:* an indistinct central endocardial echo that can be delineated by using echographic contrast material as an endocardial border and can be confirmed by using another beam angle and recording a distinct echo in this location.
3. *Off-axis echo:* any echo reflected from a source outside of the central beam that appears in the echogram to be in the central beam but in a different plane from its anatomic location.
4. *Intraseptal reflector:* an echo reflected from an intraseptal structure, such as a blood vessel wall.
5. *Septal thickness variation:* Any variation recorded in the thickness measurement between two central endocardial echoes.
6. *Septal contour variation:* variation in septal contour occurring when the position of the septum relative to the transducer varies but the thickness is unchanged.

To document the existence of the various echographic phenomena, we made the following assumptions in interpreting the echographic contrast study:

1. An echographic contrast agent that is contiguous with a distinct echo in the vicinity of the septal border delineates the central endocardial echo from off-axis and tricuspid valve echoes.
2. An echographic contrast agent delineates echoes within the central portion of the beam as septal borders (Fig. 1).
3. Off-axis echoes do not reflect more sound than the center endocardial echo, but intraseptal reflectors may, if the beam angle favors the intraseptal reflector.

Results

Echographic contrast and sound reflection: In evaluating our study, we believed it important to determine if the echoes identified as endocardial echoes with the echographic contrast agent were in the central or peripheral portion of the ultrasonic beam. Using the cadaver model, we positioned the transducer so that it was perpendicular to a section of the septum covered by the width of the beam. In this situation, echoes reflected from the periphery of the beam would appear to be within the central beam but further from the trans-

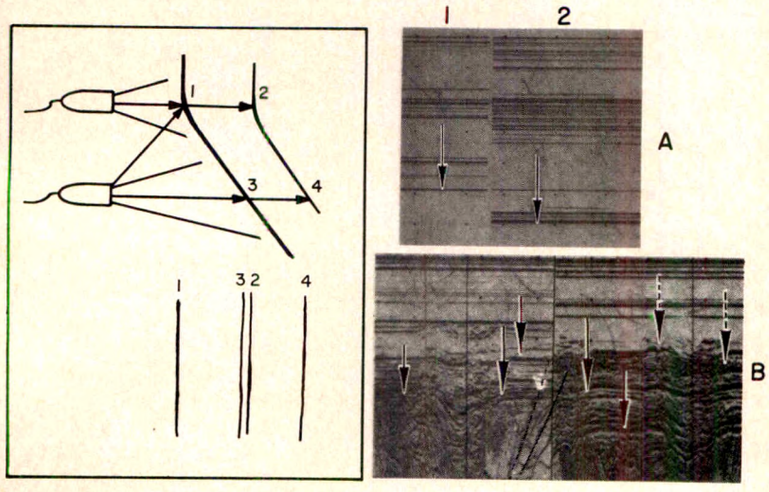

FIGURE 3. Septal contour variation. The drawing **(left)** shows how septal contour variation can create multiple reflecting surfaces. If the transducer is positioned to cross the septal border at points 1 and 2, two single echoes may be recorded. If the transducer is positioned to cross the septum at points 3 and 4, and the width of the beam allows reflection from points 1 and 2, a confusing series of echoes may be recorded (1-3-2-4). **A** represents septal echograms taken at two sites to illustrate a change in contour but not in thickness. The **arrows** identify the posterior endocardial echoes. **B** shows a change in contour between recordings 1 and 2. The **solid arrows** identify septal borders; the **dashed arrows** show off-axis echoes related to the change in contour. The echographic contrast agent identifies the posterior endocardial septal echo.

ducer than the central beam echoes. In the case of the right septal border, the peripheral beam echoes would appear to be within the septal echogram. Peripheral beam echoes from the left septal border would appear to be within the left ventricular cavity.

To identify the border echo within the central beam, we positioned a needle perpendicular to the septum in the central portion of the beam just in front of the septal border. We identified the border echo within the central beam as the echo just behind the needle. We then moved the needle to the periphery of the beam just in front of the left and right septal borders (Fig. 1). In the case of the right septal border, the moving needle echo appeared to pass through the central beam border echo and into the septal substance. The moving needle echo, when positioned at the periphery of the beam along the left septal surface, appeared to be within the left ventricular cavity when compared with the previously identified central border echo. When the echographic contrast agent was injected into the right and left ventricular cavities (Fig. 1), the needle echoes at the periphery of the beam were distinctly separated and behind the borders delineated with the contrast agent. We believe that this observation confirms the fact that the needle positioned within the central beam and the echographic contrast agent used to identify a border echo closely approximate each other. In the patient studies we assumed that the echographic contrast agent identifies border echoes within the central beam.

Spurious off-axis echoes: *Figure 2 shows an example of off-axis echoes.* In the cadaver study, a needle was used to identify the central beam endocardial echo. Echoes that reflected less sound and appeared within the left ventricular cavity were identified as off-axis echoes. In the patient study, an echographic contrast agent was used to identify the central endocardial echo. Three echograms are shown that were recorded at two different beam angles. The middle recording (B) shows distinct septal walls, and the thickness of the septum matches the septal thickness determined with the echographic contrast agent. The other two recordings (A and C) reveal intracavitary echoes; the contrast agent passes through the intracavitary echoes, documenting their off-axis origin. If the off-axis echoes are misinterpreted as septal borders, the septal measurement will be thicker than the actual dimension.

Variation in contour is a septal characteristic that may lead to the misidentification of off-axis echoes as endocardial echoes.

Figure 3 illustrates echograms from both a cadaver and a patient, showing a septum that can be recorded in different positions relative to the transducer. The dimensions of the septum do not vary; only its position. The recording in the cadaver study was obtained by placing the transducer in two locations. In the patient study, the variation occurred when one recording was made in the third and the other in the fourth intercostal space. The variation in the septal contour, noted in the echogram, was verified with a septal angiogram. The patient study illustrates how variation in septal contour can produce confusing off-axis echoes. In the patient's echo-

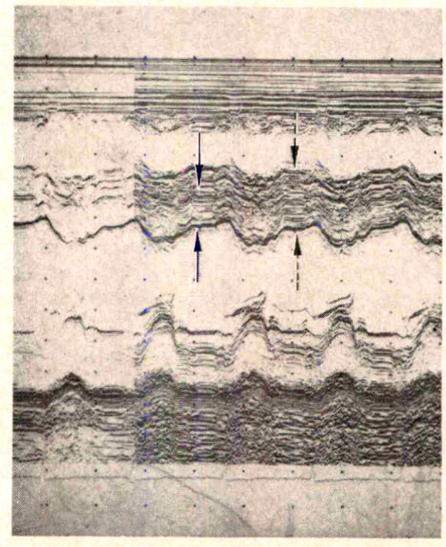

FIGURE 4. Same patient as in Figure 3. Echogram recorded before the echographic contrast study of Figure 3. The **solid arrows** outline a septal thickness consistent with the contrast studies. The **dashed arrows** show borders originally identified as endocardial echoes. ECG = electrocardiogram; IVS = interventricular septum.

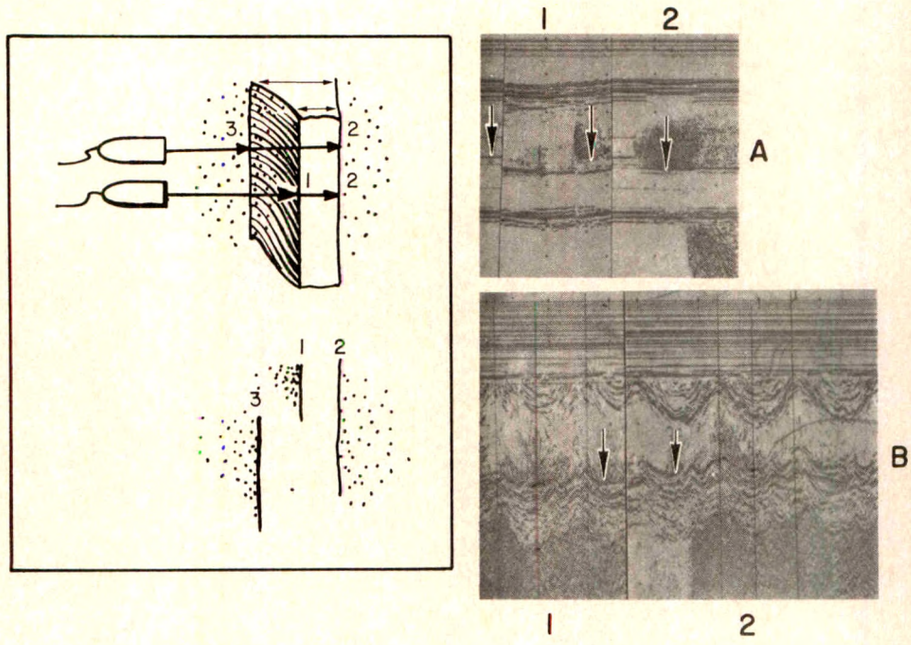

FIGURE 5. Septal thickness variation. The drawing **(left)** illustrates a change in septal thickness at different transducer positions. **A,** the two recordings show a difference in septal thickness that was confirmed with direct measurement. The **arrows** identify the endocardial surface of the right septal borders. The echographic contrast agent was used to identify endocardial echoes. **B** shows two echograms (1 and 2) indicating different values for septal thickness. Both echograms were recorded in the same interspace using standard guidelines for beam angle adjustment. The **arrows** identify the right septal surface.

gram, a septal dimension of 1.3 cm was measured when an echographic contrast agent was used to identify the central endocardial echoes. Both this measurement and the septal thickness measurement determined from the angiogram are compatible with mild septal hypertrophy. An echogram obtained before the echographic contrast study recorded a measurement of 2.0 cm (marked septal hypertrophy) (Fig. 4). In this echogram, off-axis echoes were misinterpreted as central endocardial echoes.

Septal thickness variation: *Figure 5 demonstrates variation in septal thickness in both the cadaver and the echographic contrast study.* In the cadaver model, we deliberately moved the transducer so that it would reflect an actual difference in septal measurement in a section of the septum that could be recorded with the transducer in the standard position. In the contrast study, when both central endocardial echoes were identified, a 2 mm difference in thickness measurement occurred, although both septal echograms were recorded using standard recording guidelines for septal thickness measurement.

In seven patients we obtained two or more thickness measurements with the transducer in the same interspace and the beam crossing the tips of the mitral valve. We were able to show variations in measurement as outlined in Table I. The variation in septal measurement and position, noted after spurious echoes had been eliminated, may be explained by the angle at which the beam crosses the septum or by anatomic variation in septal thickness, or both. The standard deviation noted in selected patients suggests that both the mean value and the range of measurements may help in evaluating

TABLE I

Variations in Septal Measurement in Seven Patients

Case no.	Age (yr) & Sex	Measurements (no.)	Septal Thickness (cm)			Transducer to Left Septal Surface (cm)			Transducer to Pericardium (cm)			Clinical Diagnosis
			Range	Mean	SD	Range	Mean	SD	Range	Mean	SD	
1	52M	2	1.1–1.2	. . .	. . .	4.0–5.1	. . .	. . .	12.8–13.6	. . .	. . .	MS; MR
2*	33M	3	1.1–1.5	. . .	. . .	4.4–4.8	. . .	. . .	11.6–12.0	. . .	. . .	Acromegaly; right and left CA fistula
3*	36M	4	1.0–1.3	1.1	0.14	5.1–6.0	5.3	0.37	11.4–11.9	11.7	0.24	Anomalous origin RCA
4	42F	5	0.6–0.8	0.7	0.09	4.7–5.2	5.9	0.43	10.6–10.9	10.7	0.01	Chest pain
5	31M	2	0.8–1.0	. . .	. . .	6.9–7.0	. . .	. . .	13.4–13.4	. . .	. . .	ASHD
6*	45M	7	1.0–1.5	1.28	0.2	4.0–4.6	5.5	1.1	11.1–12.0	11.8	0.41	MS; MR; pulm hypertension
7	57F	5	1.3–1.4	1.36	0.05	4.5–4.7	4.6	0.1	11.4–11.4	11.4	. . .	ASHD; inf MI

* These patients had septal variation of more than 2 mm, and separate measurements were made showing different beam crossing pathways (variation in measurement with variation in septal position).

ASHD = arteriosclerotic heart disease; CA = coronary arterial; Inf MI = inferior wall myocardial infarction; MR = mitral regurgitation; MS = mitral stenosis; pulm = pulmonary; RCA = right coronary artery; SD = standard deviation.

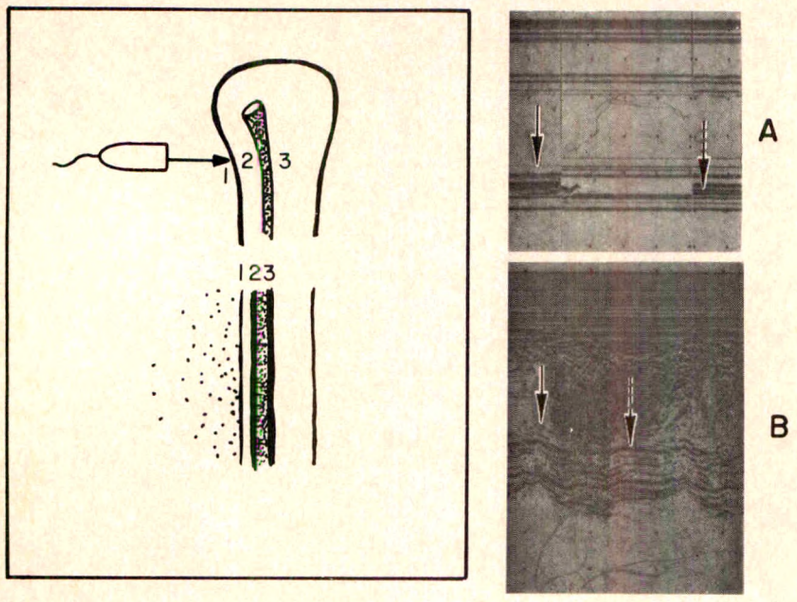

FIGURE 6. Intraseptal reflectors. The diagram **(left)** illustrates a branch of the left anterior descending coronary artery **(shaded area)** that may produce a distinct intraseptal echo. In **A** the intraseptal echoes disappear when the arterial branch is removed. The **solid arrow** indicates the endocardial echo identified with the needle reflector. A stronger intraseptal reflector is indicated by the **dashed arrow. B** shows an intraseptal reflector **(dashed arrow)** that reflects more sound than the faint endocardial echo identified with an echographic contrast agent.

septal thickness measurements in individual patients.

Intraseptal specular reflectors that may appear as the endocardial echo: *Figure 6 shows an example of an intraseptal specular reflector.* The origin of two of the intraseptal echoes was determined in the cadaver study. The intraseptal echoes were located in the same area as a septal branch of the anterior descending artery. Once the blood vessel was removed, the intraseptal echoes in the vicinity of the penetrating vessel disappeared. These echoes reappeared when the section was replaced. We were careful to preserve the endocardial surfaces as sources of off-axis intraseptal echoes and believed that this approach would allow us to separate intraseptal reflectors from off-axis echoes. In the patient study, we were unable to remove a septal section and therefore relied on an indirect method of separating off-axis echoes from those reflected from an intraseptal reflector. We excluded the off-axis reflector as the source of the intraseptal echo because this echo reflected more sound than the central endocardial echo, as defined with the echographic contrast studies. Some investigators may question whether intraseptal reflectors can reflect more sound than the central endocardial echo. The documentation of endocardial dropout establishes that this may occur at selected beam angles.

Figures 7 and 8 illustrate endocardial echo dropout. In the cadaver model (Fig. 7), a needle identifies the central endocardial echo. After the needle is removed, no echo is present. Without the needle to identify the wall, two other specular reflectors are noted that could be confused with an endocardial echo. A similar observation was made using echographic contrast techniques. In addition to an endocardial echo, there is an intraseptal echo that could be misinterpreted as the endocardial echo that "dropped out." The endocardial echo that forms the posterior septal border is not visible as a persistent echo. Only faint, intermittent recordings of this echo are noted. Figure 8 shows a similar finding and illustrates the specular qualities of endocardial echo reflection.

Intraventricular reflectors: Anatomic analysis of the interventricular septum reveals a close anatomic relation between the tricuspid valve apparatus and the right septal surface. We assumed that the tricuspid valve echo would appear as a specular reflector and be enveloped by the echographic contrast agent because of its intraventricular position. An example of an echo that met this criterion is shown in Figure 9A. A similar echo was identified in 7 of the 13 patients studied. In evaluating these seven patients, we observed four consistent characteristics of the tricuspid valve echo that helped us to identify it without use of the contrast agent: (1) It appears as a specular reflector; (2) it does not have a group of closely associated echoes moving in parallel; (3) it is best recorded in the late diastolic phase (often dropping out in early diastole); and (4) its motion is unique compared with that of the surrounding echoes. The only echoes identified within the left ventricular cavity met the definition established for off-axis echoes.

Identification of endocardial echoes: Such identification becomes more difficult once one realizes that specular reflectors are located within the septum and right ventricular cavity. Because specular reflectors, such as the endocardial echoes, have a narrow reflecting angle, it is possible that small changes in beam angle will cause these echoes to "drop out" completely or to appear only as faint reflectors. If we identified the right septal endocardial echo as the most intense border-forming echo, closely associated with a series of echoes moving in parallel, we could correctly identify the right septal endocardial echo in 11 of the 13 patients. Although this proved to be the most useful criterion for delineating this echo, it was not always reliable. In identifying the left septal echo, Feigenbaum[5] pointed out that, in addition to its specular nature, the left septal endocardial echo has a prominent notch in end systole. In our study this notch was not visualized in each recording, but it

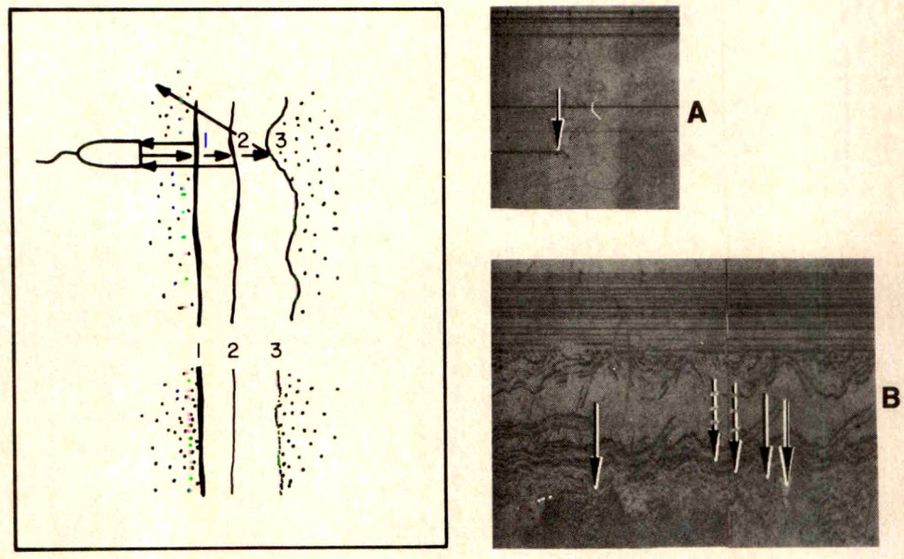

FIGURE 7. Endocardial dropout. The diagram **(left)** illustrates an intraseptal reflector at a more perpendicular angle to the ultrasonic beam than to the endocardium. In this situation echoes 1 and 2 may be visible but echo 3 may "drop out." In **A** the **arrow** identifies a needle echo positioned next to the endocardium, which has "dropped out" (absent echo after needle removed). In **B** the **solid arrow,** next to the echographic contrast agent, identifies the endocardial echo. The **two dashed arrows** identify intraseptal reflectors. The **first solid arrow to the right of the dashed arrows** identifies septal muscle. The **solid arrow furthest to the right** locates the position of the endocardial echo that "dropped out."

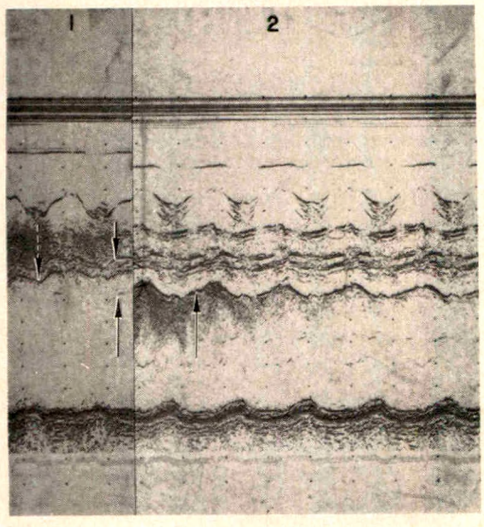

FIGURE 8. Complete "dropout" of the posterior septal endocardial echo at a slight change in beam angle consistent with a narrow reflecting angle **(solid arrows** identify endocardial surfaces). The **dashed arrow** shows an intraseptal reflector that persists in both recordings (1 and 2).

would be identified in all 13 patients if repeated tracings were evaluated. In each case, the echo with the prominent notch corresponded to the left septal endocardial echo identified with the echographic contrast technique.

Discussion

The data from the cadaver and patient studies indicate that both endocardial misidentification and anatomic variation in septal thickness should be considered by the echocardiographer in reporting septal thickness measurements. Although the frequency of these problems has not been determined, they should be suspected especially in patients whose echographic findings do not coincide with other clinical data. The cadaver model allowed direct identification of the central endocardial echo and the origin of an echo as an off-axis echo or as an intraseptal reflector. The echographic contrast studies utilized an indirect method of structure identification and necessitated the assumptions given in the Methods section. Although these assumptions can be questioned, they appear to be valid because the findings of the patient studies were consistent with those of the cadaver investigation. In addition, other investigators,[6–8] by comparing their results with other standards of measurement, have been able to substantiate that echographic contrast agents accurately define cardiac echo sources.

Misidentification of endocardial echoes: Our investigation is not the first study to consider endocardial misidentification. Roelandt et al.[3] mentioned that off-axis echoes can be confused with endocardial echoes, but their observation was not documented with echographic contrast or cadaver model studies. Their proposed solution—identifying the central endocardial echo as the strongest reflector in the vicinity of the cardiac border—did not prove reliable in either our cadaver or patient studies. The criteria outlined in the Results section may be helpful in accurately identifying endocardial echoes, but a prospective correlative study is required to establish further the reliability of this approach.

Previous investigators[9] have reported that the echoes of the tricuspid valve apparatus can be distinguished from those of the right septal border by an anterior systolic motion. Our studies, using echographic contrast techniques, indicate that, although the motion of tricuspid echoes does differ from that of septal echoes, this difference may vary from patient to patient. We believe

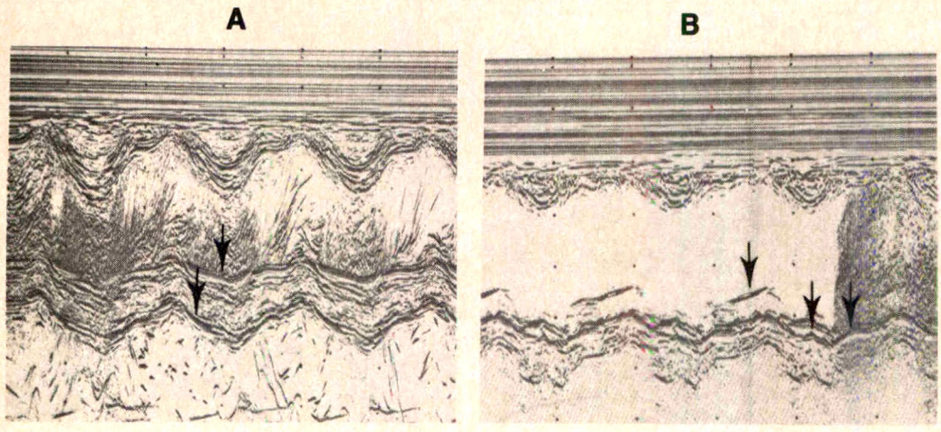

FIGURE 9. Echograms. **A** shows the echographic contrast agent that delineates the right septal border as a prominent peripheral echo with closely associated myocardial echoes. **B** shows an intraventricular echo **(top arrow)** that is clearly separated from the right border echo **(lower arrows)**. Note the close association of the right border echo with the myocardial echoes.

that describing a series of characteristics of this echo may be more helpful in identifying it. Further studies are needed to test this hypothesis.

Variations in septal thickness measurement: Our study also evaluated variations in septal measurement that might occur because of changes in anatomic thickness. Previous references to this problem have been made,[10] but we are not aware of any attempt to document such changes using the established guidelines to minimize variations in septal measurements. Our initial observation indicates that changes of 1 to 5 mm, related to variation in beam angle or anatomic thickness, or both, can occur. The effect of this variation on the determination of septal thickness measurements needs to be evaluated in further studies.

Implications: The echocardiogram offers the clinician a valuable noninvasive tool for cardiac diagnosis and measurement of septal thickness. Previous studies have established the reliability of these methods. Recognition of the factors outlined here should help the investigator design studies to improve the reliability of the echographic measurements and should help the echocardiographer to be aware of errors related to technical recording factors.

References

1. **Feigenbaum H:** Echocardiography, edition 2. Philadelphia, Lea & Febiger, 1976, p 27; 67–78
2. **Gramiak R, Waag RC:** Cardiac Ultrasound. Saint Louis, CV Mosby, 1975, p 11
3. **Roelandt J, van Dorp WG, Bom N, et al:** Resolution problems in echocardiology: a source of interpretation errors. Am J Cardiol 37:256–262, 1976
4. **Popp RL, Filly K, Brown OR, et al:** Effect of transducer placement on echocardiographic measurement of left ventricular dimensions. Am J Cardiol 35:537–540, 1975
5. **Feigenbaum H:** Echocardiography. Philadelphia, Lea & Febiger, 1972, p 120
6. **Feigenbaum H, Stone JM, Lee DA, et al:** Identification of ultrasound echoes from the left ventricle by use of intracardiac injections of indocyanine green. Circulation 41:615–621, 1970
7. **Gramiak R, Shah PM, Kramer DH:** Ultrasound cardiography: contrast studies in anatomy and function. Radiology 92:939–948, 1969
8. **Kerber RE, Kioschos, JM, Lauer RM:** Use of an ultrasonic contrast method in the diagnosis of valvular regurgitation and intracardiac shunts. Am J Cardiol 34:722–727, 1974
9. **Kotler MN, Segal BL, Mintz G, et al:** Pitfalls and limitations of M-mode echocardiography. Am Heart J 94:227–249, 1977
10. **Devereux RB, Reichek N, Klunder PJ:** Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation 55:613–618, 1977

· In Liquid Potassium Therapy

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Each effervescent tablet in solution supplies 50 mEq potassium as bicarbonate and citrate.

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- Cost is less than a diet of potassium-rich foods.

*See Prescribing Considerations

Prescribing Considerations

Indications: K-LYTE DS, is an oral potassium supplement for therapy or prophylaxis of potassium deficiency. It is particularly useful when thiazide diuretics, corticosteroids, or severe vomiting and diarrhea cause excessive excretory potassium losses; and when dietary potassium is low. Carefully monitored, K-LYTE DS may also be useful for potassium replacement where digitalis intoxication results in cardiac arrhythmias.

Contraindications: Impaired renal function with oliguria or azotemia; Addison's disease; hyperkalemia from any cause.

Warnings and Precautions: Since the amount of potassium deficiency may be difficult to determine accurately, supplements should be administered with caution, and dosages adjusted to the requirements of the individual patient. Potassium intoxication rarely occurs in patients with normal kidney function. Symptoms of potassium intoxication are variable. They include listlessness, mental confusion, and tingling of the extremities. Frequent checks of the clinical status of the patient, ECG, and serum potassium level are desirable. In established hypokalemia, attention should also be directed toward other potential electrolyte disturbances. Potassium supplements should be given cautiously to digitalized patients and such patients should be monitored by ECG for cardiac irregularities. To minimize the possibility of gastrointestinal irritation associated with the oral ingestion of concentrated potassium salt preparations, **patients should be carefully directed to dissolve each dose completely in the stated amount of water.**

Adverse Reactions: Nausea, vomiting, diarrhea, and abdominal discomfort may occur with the use of potassium salts.

Dosage and Administration: Adults: 1 tablet completely dissolved, 1 to 2 times daily, depending upon the requirements of the patient: 1 tablet (50 mEq. potassium) in 6 to 8 ounces of cold or ice water. The normal adult daily requirement is approximately 50 mEq. of elemental potassium.

NOTE: It is suggested that K-LYTE DS be taken with meals and sipped slowly over a 5-10 minute period.

How Supplied: K-LYTE DS effervescent tablets (orange or lime flavors) are available in cartons of 30 individually foil-wrapped tablets. **Also available,** K-LYTE (25 mEq. potassium) effervescent tablets (orange or lime flavors) in cartons of 30 and 250.

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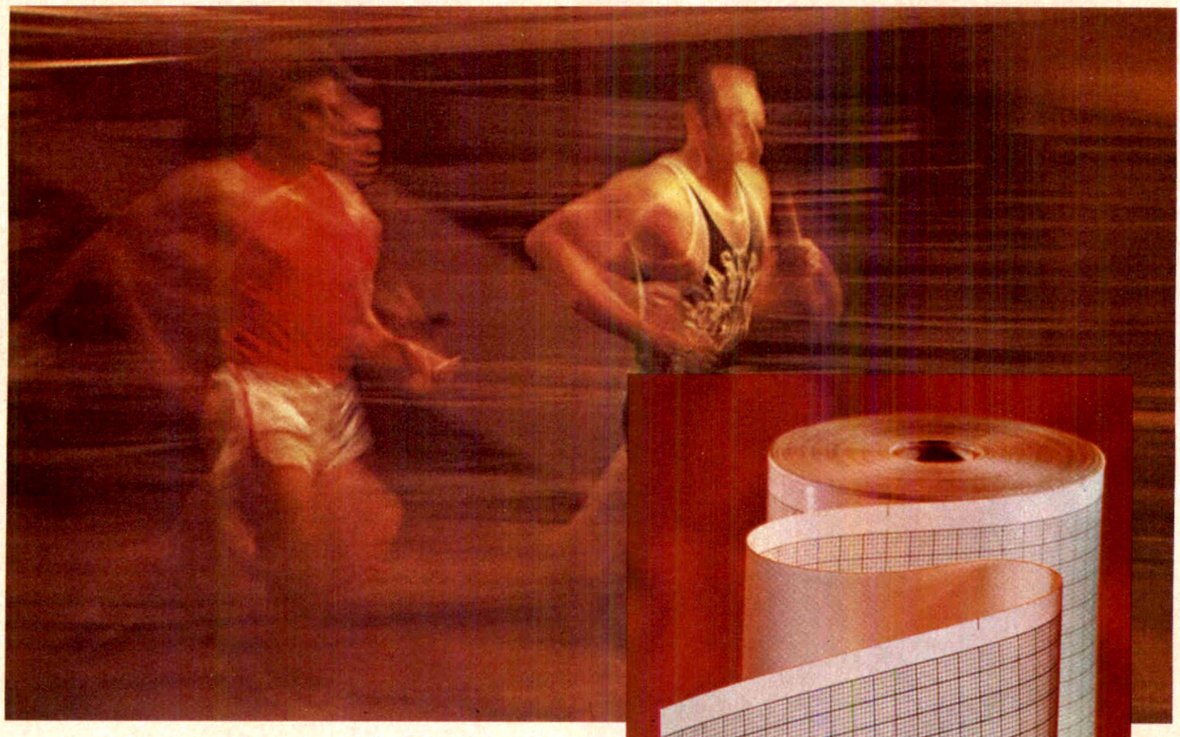

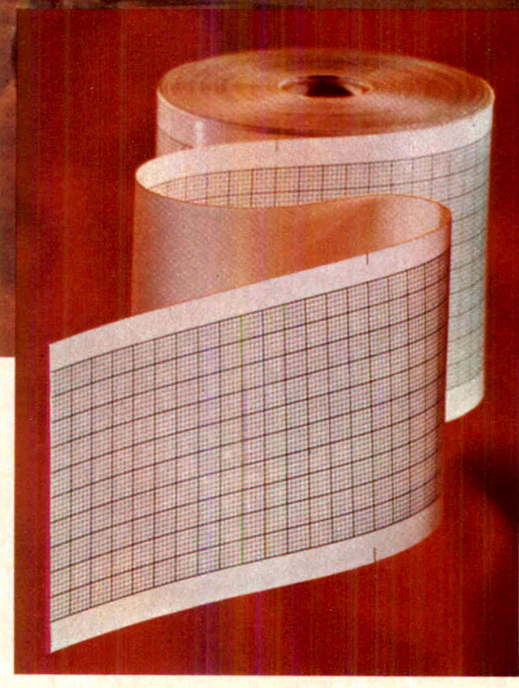

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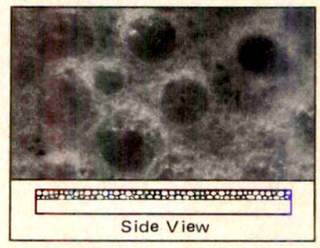

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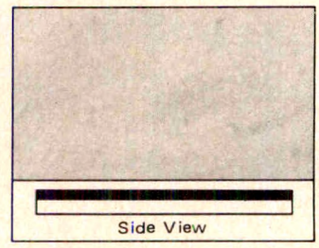

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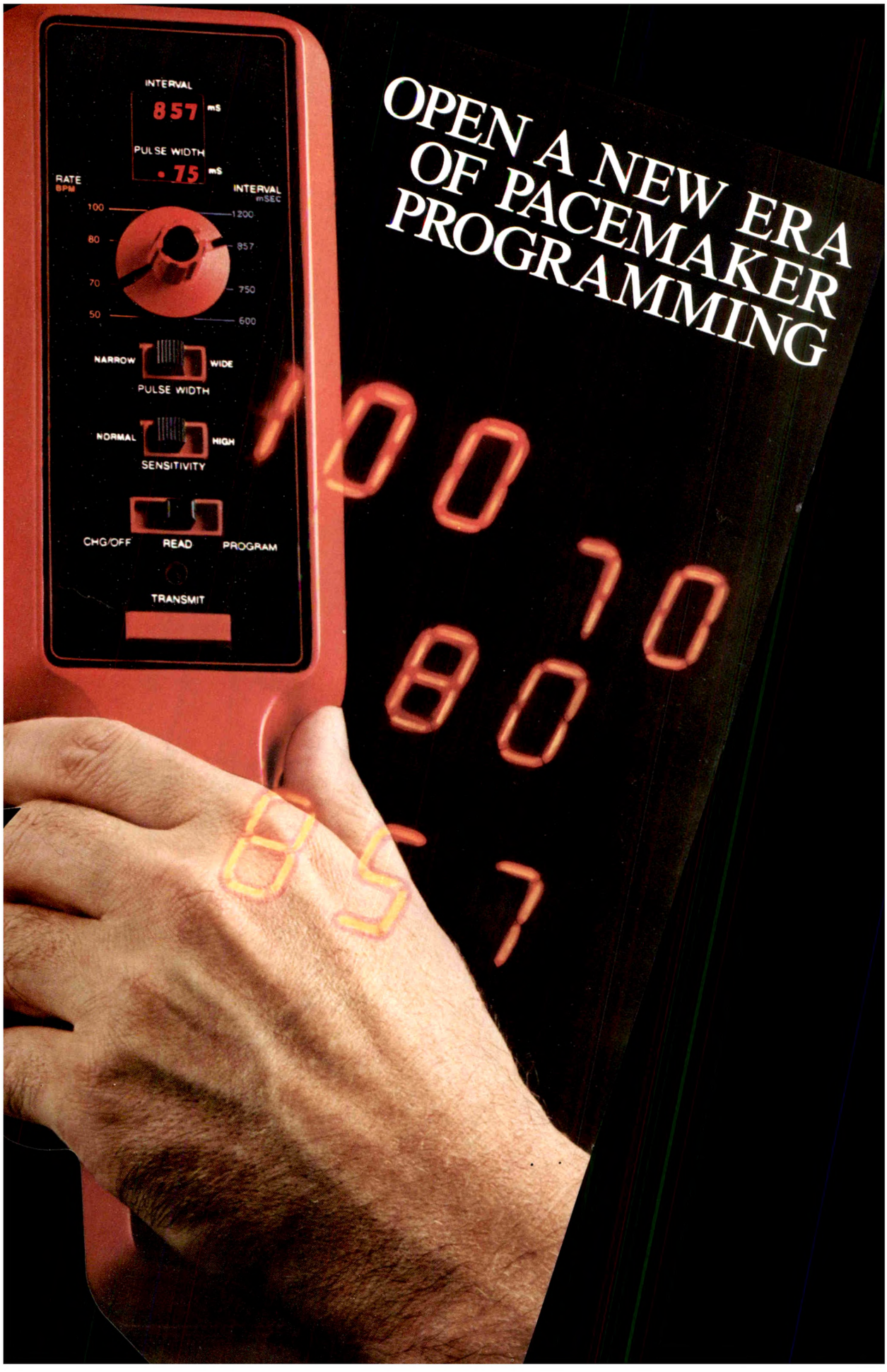
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READ
PROGRAM
TRANSMIT
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80
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MMABLE PACING SYSTEM BACK TO YOU

LITHICRON-F PACER PROGRAMMER FUNCTIONALLY AND ESTHETICALLY SUPERIOR

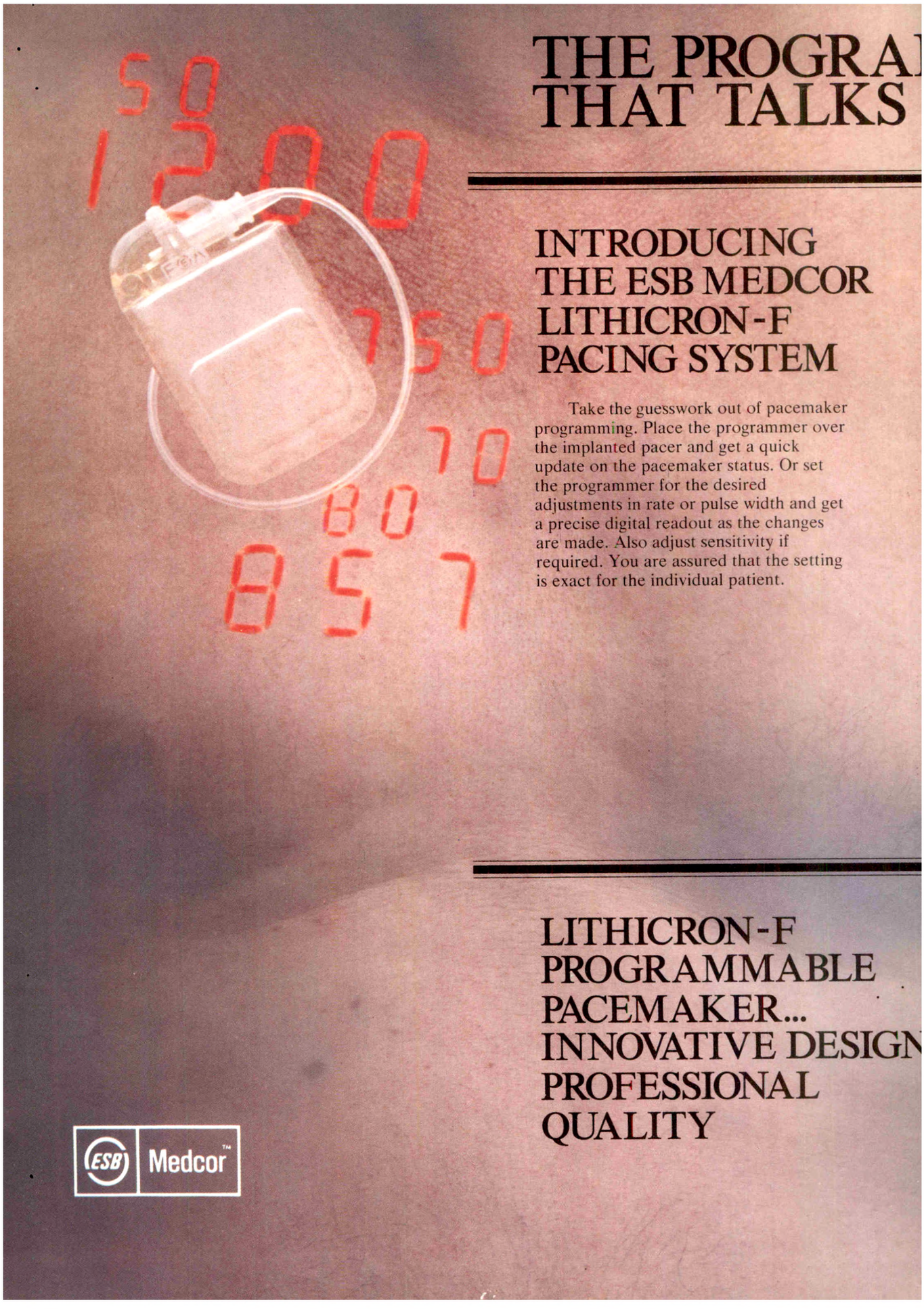
Beautifully designed...lightweight... compact...cordless...non-invasive ...latest in electronic programming (non-magnetic)...provides information directly from the pacer...relays new commands from the physician.

Supplies accurate digital readout of actual pacer rate and pulse width...provides sensitivity adjustment capability for problem cases...simply select new operating parameters, transmit the data, and the pacer is reprogrammed.

Powered by rechargeable battery or A.C. operation via the charger...permits freedom of movement in the office, treatment room or operating room... eliminates danger from electrical grounding hazards...can be used to check the pacemaker prior to implantation while still in its sterile package.

Ingenious, functionally designed programmable pacemaker..."talks" with the Lithicron-F Programmer...relays information about pacer rate and pulse width...responds instantly to commands given through the programmer.

Assembled from ultra-high reliability components...CMOS hybrid circuitry increases reliability and reduces pacer size...biocompatible titanium case... redundant hermetic sealing (power cell and electronics individually hermetically sealed within outside case)...not susceptible to external interference... potential longevity ranges to 15 years depending on lead, pacing rate and pulse width setting.



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Take the guesswork out of pacemaker programming. Place the programmer over the implanted pacer and get a quick update on the pacemaker status. Or set the programmer for the desired adjustments in rate or pulse width and get a precise digital readout as the changes are made. Also adjust sensitivity if required. You are assured that the setting is exact for the individual patient.

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The ESB Medcor Pacer-Check System enables the physician to evaluate pacer performance and other patient data by means of a conventional telephone.

The Pacer-Check System consists of two components: a portable patient transmitter and a physician's receiver. The receiver provides an ECG strip indicating pacer artifacts for determination of capture and sensing. In addition, a digital readout of the pacer rate, interval and pulse width is displayed.

The Pacer-Check Monitoring System provides the clinician with accurate and timely data by phone in order to provide maximum pulse generator longevity, detection of pacemaker malfunction, prevention of premature pulse generator replacement, and promotion of patient safety.

For additional information about any of the ESB Medcor systems contact your ESB Medcor representative or call:

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The slender profile of the L-40 makes lead placement easier and exact.

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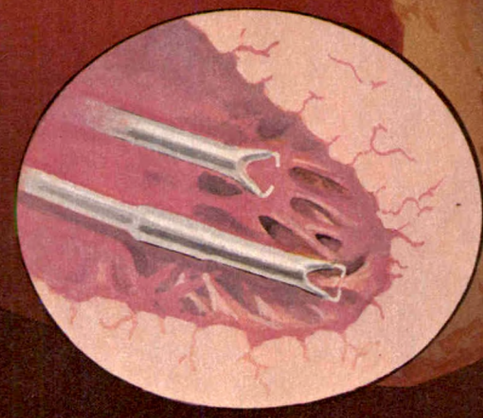


For the PVD patient, walking can be productive instead of just painful.

The Role of Walking

Exercise-induced pain is a cardinal symptom of Peripheral Vascular Disease. Often, because of intermittent claudication, patients may tend to exercise...even to walk...as little as possible.

Studies† have demonstrated that a program of regular walking exercise can significantly extend the distance and time these patients can walk without claudication. In one study walking exercise of one hour daily has been shown to effect noticeable improvement in a month. After six months, pain-free walking increased to twice that of pre-exercise levels.

Investigators have attributed the improvement to vasodilating effects of exercise, increased venous return and development of the collateral circulation. It is clear that exercise produces a tolerance for more exercise, and a program of regular walking, in the absence of any contraindications, appears to be an appropriate measure in the management of Peripheral Vascular Disease.

The Value of Proper Gait

Patients often compensate for claudication in calf muscles by adopting a shuffling gait. This "shuffling" utilizes calf muscles only minimally.

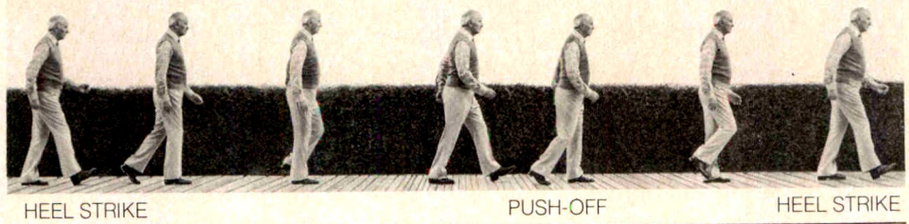
The diagram on this page illustrates the normal gait—described as "heel-and-toe" walking. Patients who are encouraged to become more conscious of their gait and to walk properly will utilize calf muscles to a greater degree—and maximize the therapeutic effects of a prescribed walking program.

The Role of Arlidin® (nylidrin HCl)

Arlidin improves blood flow by dilating responsive vessels in skeletal muscles. The symptoms of ischemia may therefore be relieved thus encouraging the patient to begin or continue with an appropriate exercise program.

Furthermore, Arlidin maintains mean arterial pressure, thus maximizing delivery of blood to ischemic areas and minimizing the risk of postural hypotension. Its vasodilating effect in skeletal muscles and maintenance of mean arterial pressure make Arlidin an appropriate adjunct to other measures—such as walking—in the management of Peripheral Vascular Disease.*

PROPER HEEL-AND-TOE WALKING



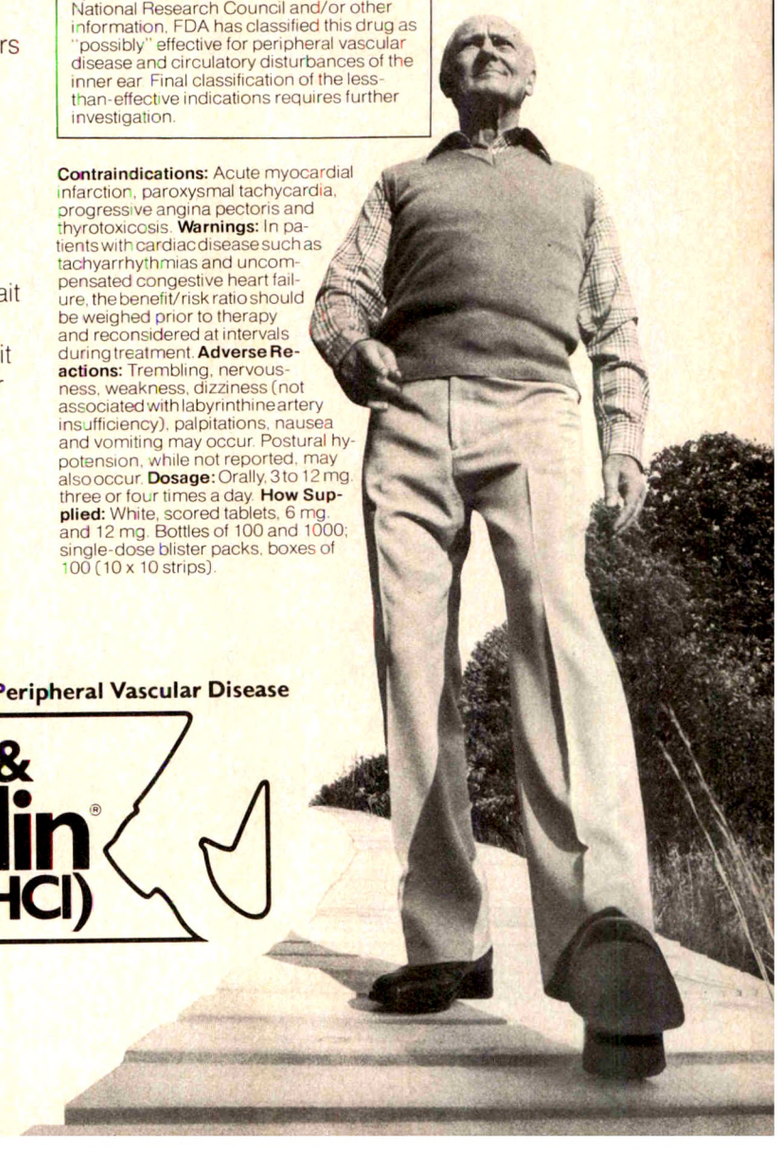
HEEL STRIKE PUSH-OFF HEEL STRIKE

You can obtain a more detailed version of this chart, explaining heel-and-toe walking to patients, from your USV Representative or by writing to Medical Department, USV Laboratories Inc., Tuckahoe, N.Y. 10707.

Brief Summary

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified this drug as "possibly" effective for peripheral vascular disease and circulatory disturbances of the inner ear. Final classification of the less-than-effective indications requires further investigation.

Contraindications: Acute myocardial infarction, paroxysmal tachycardia, progressive angina pectoris and thyrotoxicosis. **Warnings:** In patients with cardiac disease such as tachyarrhythmias and uncompensated congestive heart failure, the benefit/risk ratio should be weighed prior to therapy and reconsidered at intervals during treatment. **Adverse Reactions:** Trembling, nervousness, weakness, dizziness (not associated with labyrinthine artery insufficiency), palpitations, nausea and vomiting may occur. Postural hypotension, while not reported, may also occur. **Dosage:** Orally, 3 to 12 mg. three or four times a day. **How Supplied:** White, scored tablets, 6 mg. and 12 mg. Bottles of 100 and 1000; single-dose blister packs, boxes of 100 (10 x 10 strips).



The new prescription for Peripheral Vascular Disease

Walking & Arlidin® (nylidrin HCl)

†A bibliography of published papers on therapeutic walking is available upon request.

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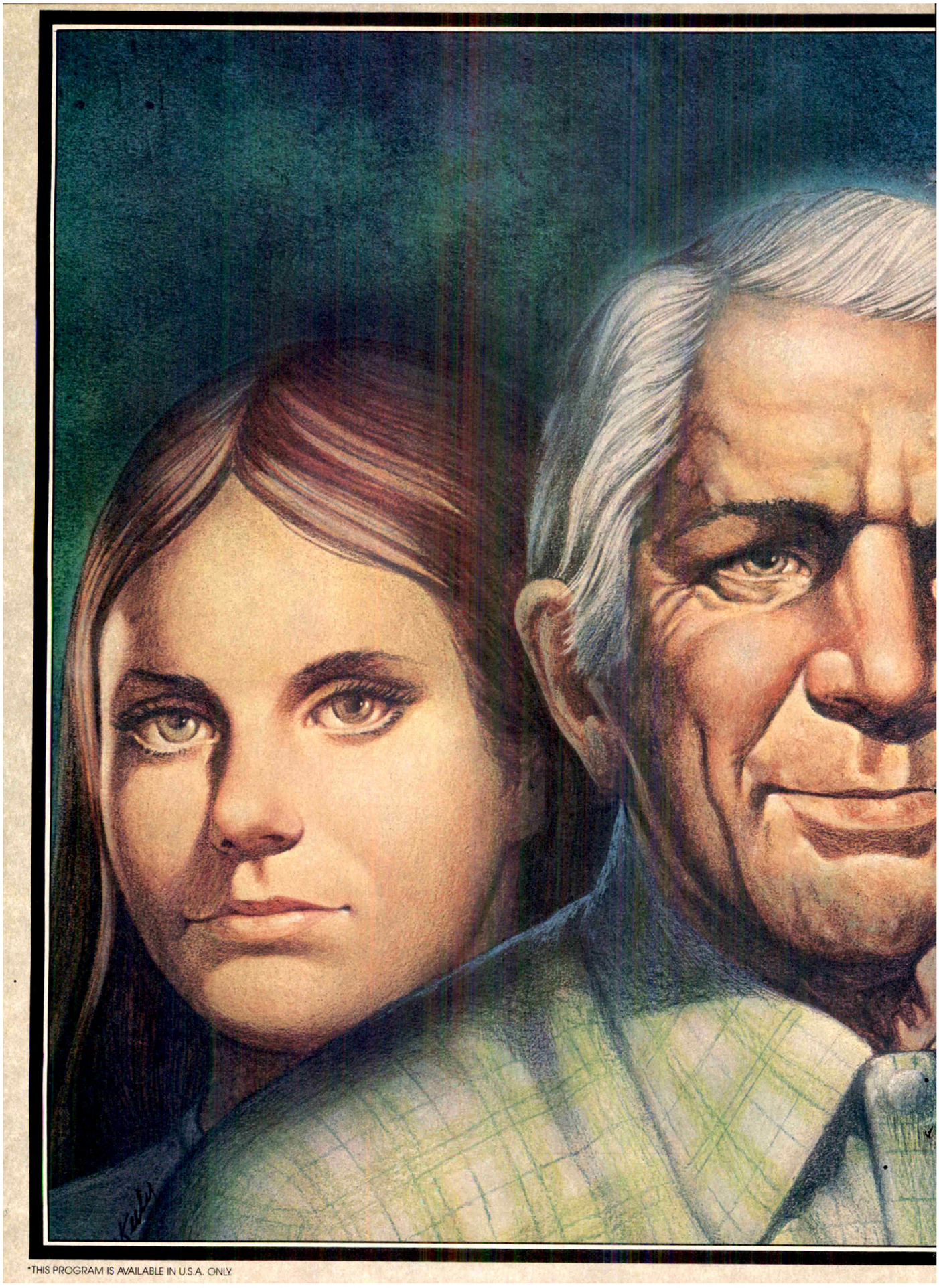
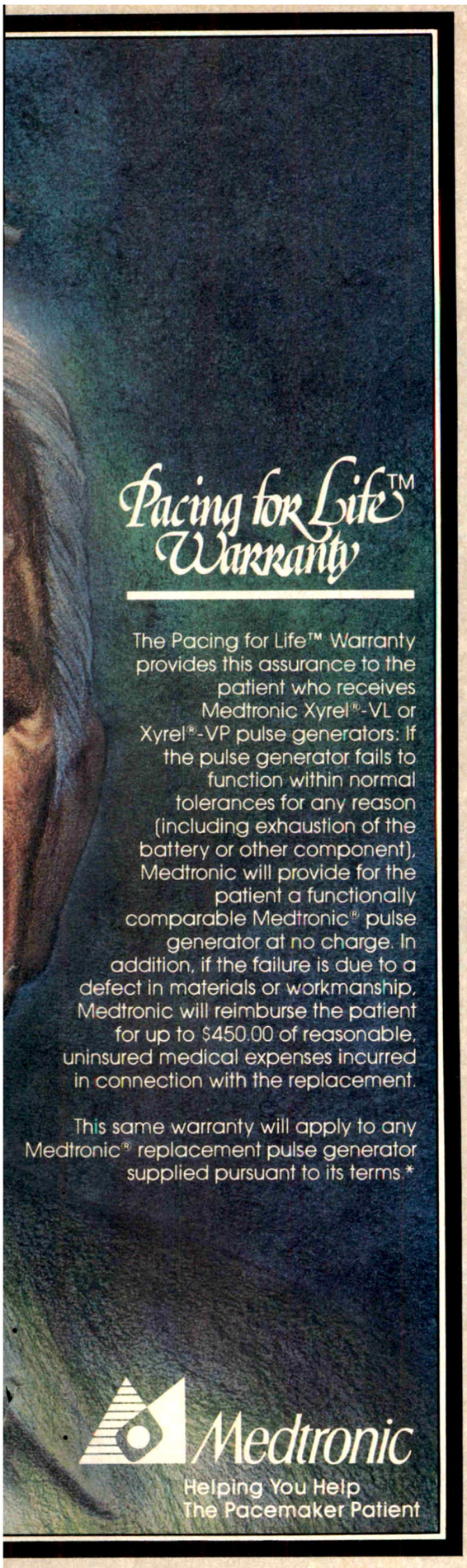


*THIS PROGRAM IS AVAILABLE IN U.S.A. ONLY



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The Pacing for Life™ Warranty provides this assurance to the patient who receives Medtronic Xyrel®-VL or Xyrel®-VP pulse generators: If the pulse generator fails to function within normal tolerances for any reason (including exhaustion of the battery or other component), Medtronic will provide for the patient a functionally comparable Medtronic® pulse generator at no charge. In addition, if the failure is due to a defect in materials or workmanship, Medtronic will reimburse the patient for up to $450.00 of reasonable, uninsured medical expenses incurred in connection with the replacement.

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Medtronic

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The Pacemaker Patient

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NOW AVAILABLE FOR YOUR PACEMAKER PATIENTS FROM MEDTRONIC®

That's right, doctor. If your patient receives a Xyrel®-VL or Xyrel®-VP pacemaker, Medtronic will provide a lifetime pacemaker replacement guarantee. If the pacemaker fails for any reason — any reason — Medtronic will replace it. Free.

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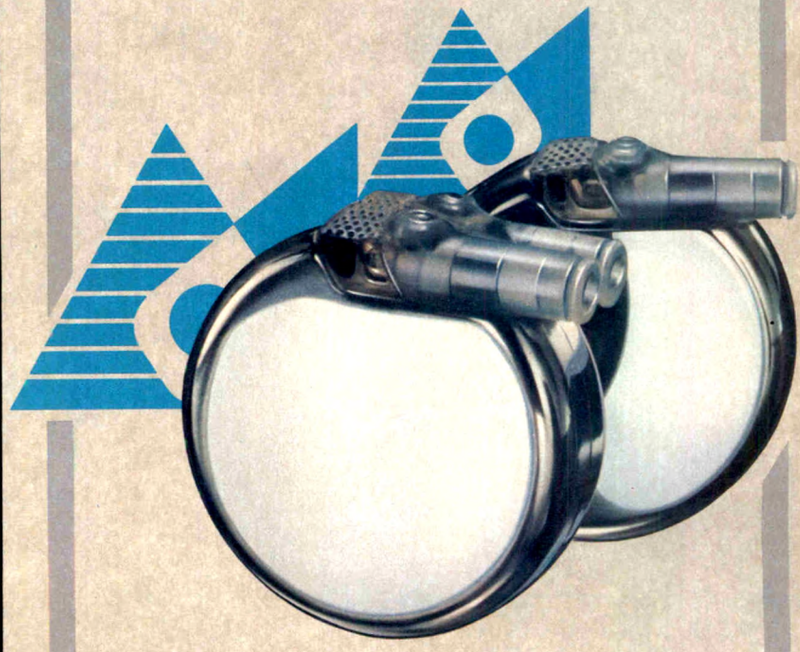

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See disclosure statement on following page.

MEDTRONIC®
IMPLANTABLE PULSE GENERATORS

INTENDED USES

Ventricular pacing using an implantable ventricular pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation or conduction disorders leading to bradyarrhythmias, tachyarrhythmias and heart block (see product labeling for detailed list of intended uses).

CONTRAINDICATIONS

There are no known contraindications to the use of pacing as a therapeutic modality for the control of heart rate. The patient's age and medical condition, however, may dictate the particular pacing systems and implantation procedure used by the physician.

WARNINGS

Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of unipolar pulse generators or bipolar pulse generators implanted in the unipolar mode because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator.

PRECAUTIONS

The physician should be aware that all pulse generators will ultimately cease to function, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, and elevated thresholds, and that proper operation may be affected by electrical interference from equipment using electrical energy, or medical complications.

SIDE EFFECTS

Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.

Medtronic

Medtronic, Inc.
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Minneapolis, MN 55418

ALDACTONE®
(spironolactone) 25 mg. tablets

WARNING
Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats (see *Warnings*). Aldactone should be used only in those conditions described under *Indications*. Unnecessary use of this drug should be avoided.

Indications: Diagnosis and treatment of primary hyperaldosteronism. Essential hypertension, edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate. Cirrhosis of the liver accompanied by edema and/or ascites. Hypokalemia.

Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, or hyperkalemia.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactone. Do not administer concurrently with other potassium-sparing diuretics.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75, and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hyponatremia may be caused or aggravated, especially when Aldactone is administered in combination with other diuretics. Transient elevation of BUN and/or mild acidosis may occur. Aldactone potentiates the effect of other diuretics or antihypertensive agents, particularly ganglionic blocking agents: therefore the dosage of such drugs should be reduced by at least 50 percent when adding Aldactone. Gynecomastia may develop and in rare instances some breast enlargement may persist. Vascular responsiveness to norepinephrine may be reduced.

Spironolactone may cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazard to the fetus. Breast feeding should be discontinued when Aldactone is being used.

Adverse Reactions: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established. Adverse reactions are usually reversible upon discontinuation of the drug.

Dosage and Administration

For primary hyperaldosteronism: 400 mg. daily for three to four weeks (long test), or for four days (short test). For preparation for surgery or for long-term maintenance therapy, 100 to 400 mg. daily.

For edema in adults: Initial daily dosage is 100 mg. in divided doses but may range from 25 to 200 mg. daily. If after five days an adequate diuretic response has not occurred, a second diuretic which acts more proximally in the renal tubule may be added. The dosage of Aldactone should remain unchanged when other diuretic therapy is added.

For edema in children: Initial daily dosage should provide approximately 1.5 mg. per pound of body weight (3.3 mg./kg.) in divided doses.

For essential hypertension: Initial adult daily dosage of 50 to 100 mg. in divided doses, alone or with diuretics which act more proximally in the renal tubule, or with other antihypertensive agents. Continue treatment for at least two weeks since maximal response may not occur before this time. Adjust subsequent dosage according to patient response.

For hypokalemia: 25 to 100 mg. daily in divided doses.

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San Juan, Puerto Rico 00936

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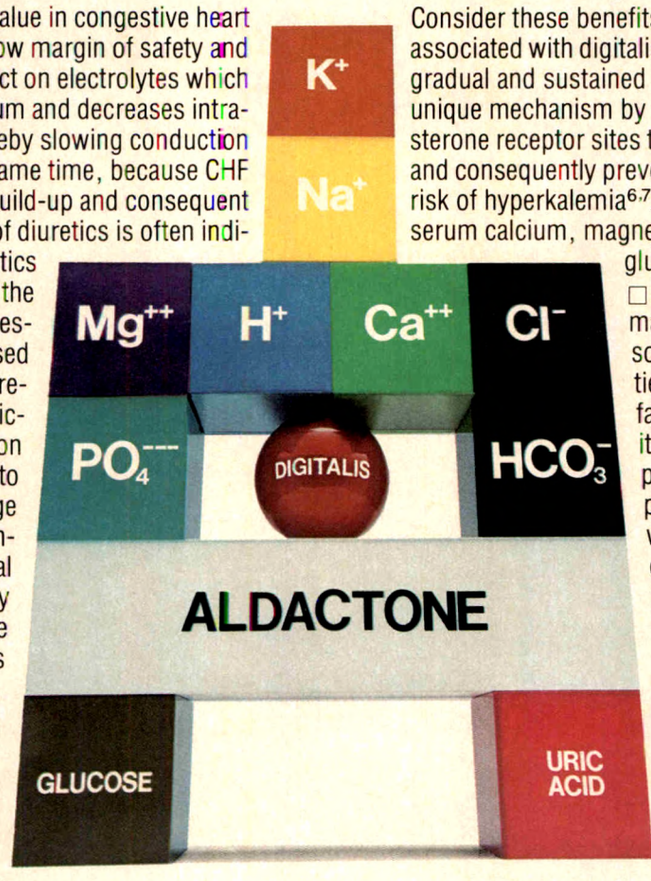
719

The Delicate Balance.

Unfortunately, electrolyte imbalance is often a problem during digitalis therapy. And most diuretics worsen the problem.

Despite its therapeutic value in congestive heart failure, digitalis has a narrow margin of safety and toxic levels produce an effect on electrolytes which increases intracellular sodium and decreases intracellular potassium, thereby slowing conduction in cardiac tissues. At the same time, because CHF encourages sodium build-up and consequent edema, concomitant use of diuretics is often indicated. □ Use of most diuretics can increase problems for the patient on digitalis, and excessive loss of potassium caused by potent diuretics is a frequent cause of digitalis toxicity.[1,2] Potassium depletion sensitizes the myocardium to digitalis and can set the stage for serious cardiac arrhythmias even with normal dosage.[3] □ Clearly, any diuretic choice should be carefully analyzed for its effect on electrolyte balance. Thiazides, for example, can induce hypokalemia, hypercalcemia, hypomagnesemia, and hypophosphatemia.[4] They can also decrease uric acid excretion and impair glucose tolerance. In treatment with furosemide, too, fluid and electrolyte imbalance is the most common form of clinical toxicity.[5]



Fortunately, concomitant diuretic therapy with Aldactone® (spironolactone) can help maintain the delicate electrolyte balance... when other measures won't do.

Consider these benefits in avoiding the problems associated with digitalis therapy: Aldactone provides gradual and sustained diuresis...works through a unique mechanism by which it competes for aldosterone receptor sites to normalize body potassium, and consequently prevents hypokalemia with limited risk of hyperkalemia[6,7]...does not adversely affect serum calcium, magnesium and uric acid levels or glucose tolerance.[7]

□ Aldactone is indicated for management of edema and sodium retention in those patients with congestive heart failure who are taking digitalis, or in the treatment or prevention of hypokalemia in patients taking digitalis, when other measures are considered inadequate or inappropriate. □ When diuretic therapy is indicated, prescribe Aldactone to help preserve the delicate balance of electrolytes during digitalis therapy.

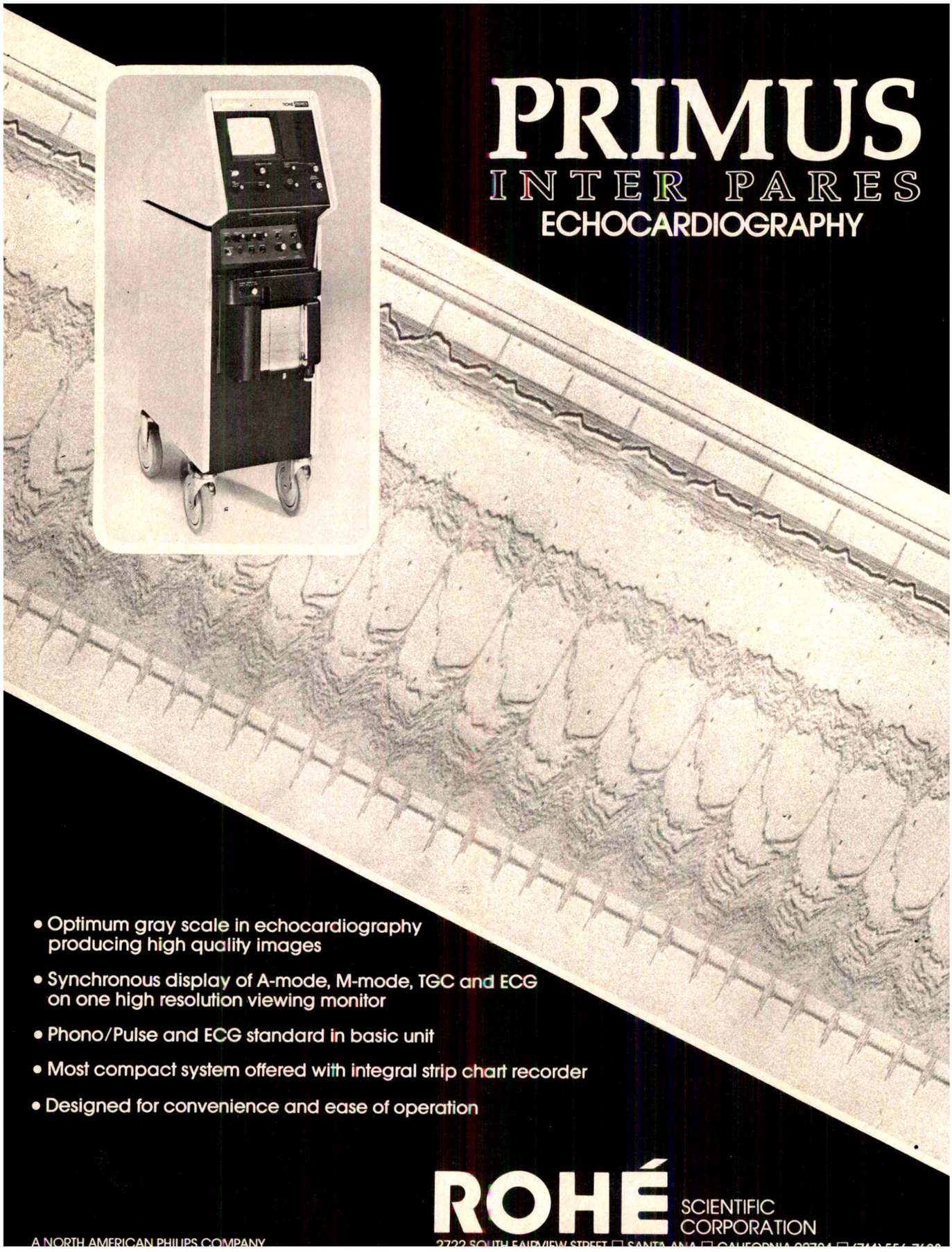
1. Kirkendall, W.M.: What's With Hypertension These Days? Consultant *11*:13-15 (Jan.) 1971.
2. Maronde, R.F.; Milgrom, M. and Dickey, J.M.: Potassium Loss with Thiazide Therapy. Am. Heart J. *78*:16-21 (July) 1969.
3. Cardiac Glycosides, Section 4, in Kastrup, E. K. (Editor): Facts and Comparisons, St. Louis, Facts and Comparisons, Inc., Jan. 1975, pp. 140-141C.
4. Weibert, R. T.: Heading Off Adverse Reactions. Thiazide Diuretics, Curr. Prescr. *3*:62-69 (Oct.) 1977.
5. Mudge, G. H., Diuretics and Other Agents Employed in the Mobilization of Edema Fluid, Chapter 39, in Goodman, L. S., and Gilman, A. (Editors): The Pharmacological Basis of Therapeutics, ed. 5., New York, Macmillan Publishing Co., Inc., 1975, pg. 836.
6. Laragh, J. H.: Diuretics in the Management of Congestive Heart Failure, Hosp. Pract. *5*:43-50 (Nov.) 1970.
7. Tobian, L. J., Jr.: The Clinical Approach to Essential Hypertension, Hosp. Pract. *10*:33-44 (July) 1975.

SEARLE

Aldactone®

(spironolactone) 25 mg. tablets

Before prescribing, please consult the complete prescribing information, a brief summary of which follows.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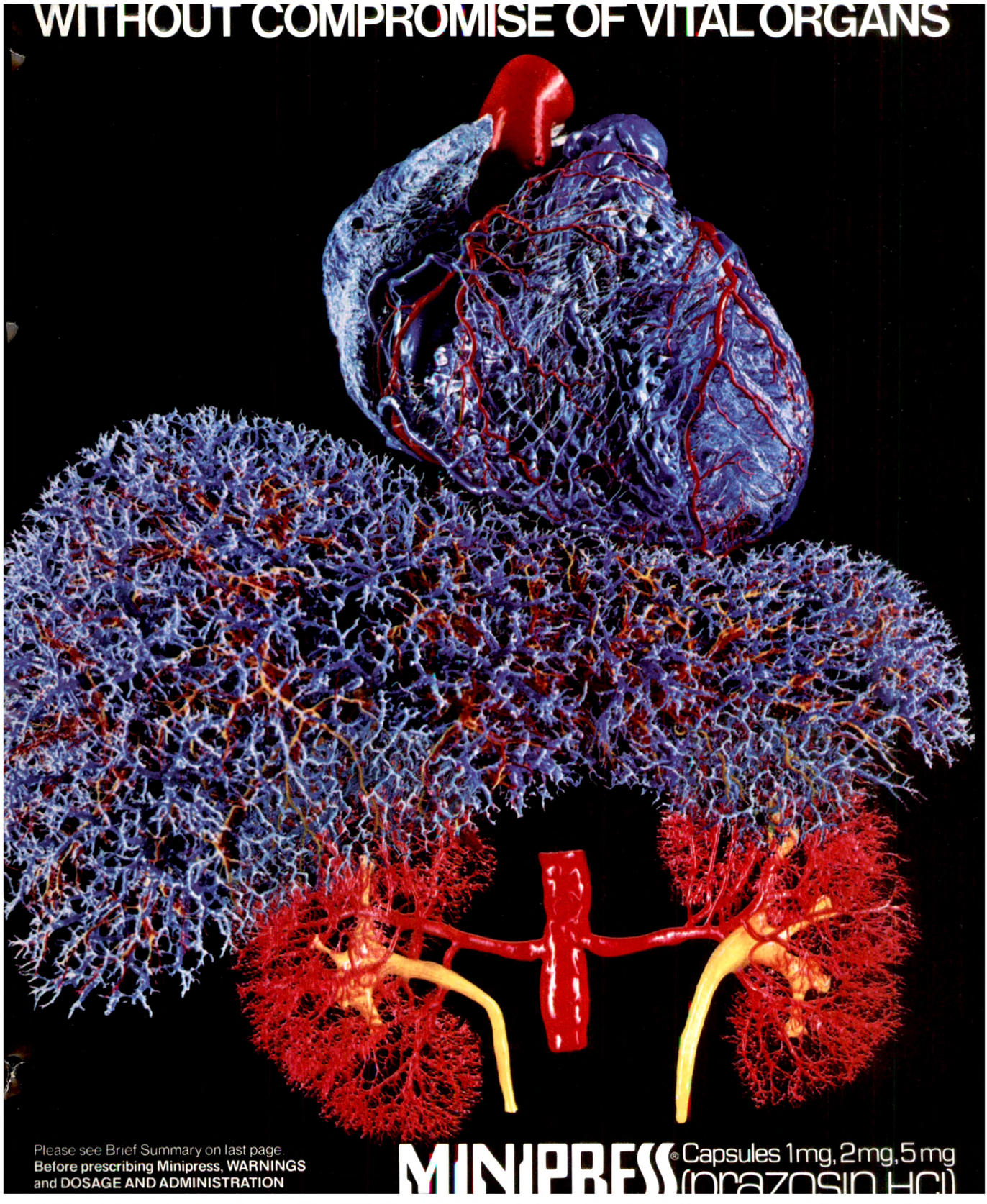
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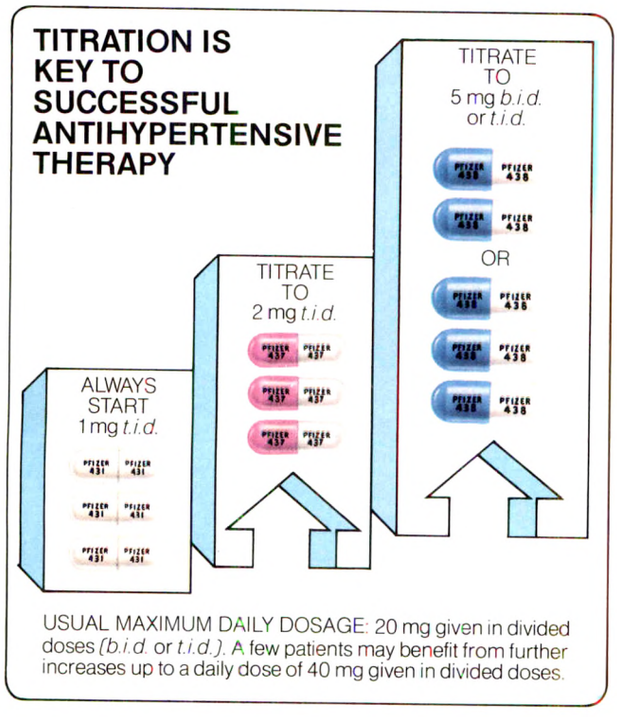
YEARS OF BLOOD PRESSURE CONTROL...WITHOUT COMPROMISE OF VITAL ORGANS

MINIPRESS® Capsules 1mg, 2mg, 5mg (prazosin HCl)



- **Initial therapy:** Whether using Minipress in combination with other agents or alone, the starting dosage is 1 mg *t.i.d.* If response is not adequate by the next visit, the dosage should be increased to 2 mg *t.i.d.*

- **Dosage titration:** Thereafter, titrations of Minipress should be carried out according to patient response. Dosage may be slowly increased to a daily maximum of 20 mg given in divided doses. Although some patients may be controlled on 1 mg *t.i.d.*, generally 6 mg to 15 mg daily will be needed in the majority of responding patients in order to achieve optimal blood pressure control.

- **Maintenance therapy:** After initial titration, patients may be maintained on a *b.i.d.* or *t.i.d.* dosage regimen.
- If optimum control is not achieved in patients receiving Minipress and a diuretic, consider adding another Step 2 antihypertensive agent.
- If optimum control is not achieved with Minipress as the initial agent, consider adding a diuretic.
- When adding a diuretic or other antihypertensive agent, Minipress dosage should be reduced to 1 mg or 2 mg *t.i.d.* and retitrated as needed.
- Available in 1-mg, 2-mg, and 5-mg capsules.

REMOVE PAGE AND FOLD ALONG DOTTED LINE AND SAVE FOR REFERENCE

BRIEF SUMMARY

MINIPRESS® (prazosin hydrochloride) Capsules *For Oral Use*

INDICATIONS. MINIPRESS (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS. MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS. The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION. The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. Higher doses usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED. MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437), and 5 mg (blue and white #438) capsules in bottles of 250, and unit-dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

Pfizer
LABORATORIES DIVISION
PFIZER INC.

Cerebrovascular Abnormalities in Postoperative Coarctation of Aorta

Four Cases Demonstrating Left Subclavian Steal on Aortography

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Fifteen children, aged 0.3 to 10.5 years (mean 3.8 years) after repair of coarctation of the aorta, underwent cerebral arteriography as part of postoperative catheterization. Four manifested central nervous system symptoms postoperatively: Two had persistent headaches, one had exercise-induced hemianopsia and one had major motor seizures. All four had greater blood pressure in the right arm than in the left and evidence of subclavian steal, with retrograde filling of the left vertebral and left subclavian arteries on selective right vertebral arteriography. Ligation of the left vertebral artery in three patients and left subclavian graft arterioplasty in one resulted in disappearance of symptoms. None of the 11 asymptomatic patients manifested cerebrovascular anomalies, and no patient in the series had berry aneurysm.

This study suggests that patients with central nervous system symptoms and a disparity of blood pressure in the arms after surgery for coarctation of the aorta should be evaluated carefully to exclude subclavian steal as the cause of the symptoms.

Cerebrovascular accidents, including rupture of a berry aneurysm and subarachnoid hemmorhage, occurring months after successful repair of coarctation of the aorta have been well documented.[1–6] However, central nervous system symptoms as the result of subclavian steal have seldom been recognized after such repair. Our experience with four patients with a subclavian steal syndrome, discovered during a study designed to evaluate the cerebral circulation in patients after repair of coarctation of the aorta, is the basis of the present report.

Material and Method

Patients: The study group consisted of 15 children who had undergone surgical repair of coarctation or interruption of the aortic arch. Parents were informed of the nature of the study, and informed consent was obtained. The patients were 4.5 to 19 years old (mean 10.8 years) and had been operated upon 0.3 to 10.5 years (mean 3.8 years) earlier. Patients with associated intracardiac defects were excluded. Preoperatively, eight patients had coarctation of the aorta without associated defects, five had associated mild aortic valve stenosis, and two patients had interrupted aortic arch distal to the origin of the left subclavian artery.

Method: Histories were obtained and all patients were examined by at least two of us. Precatheterization studies included a complete blood count, a 12 lead electrocardiogram and a chest roentgenogram. Percutaneous femoral arterial catheterization was carried out in all patients. A no. 5 French angiographic catheter was used, and selective injections of contrast material (Hypaque® 50 percent) into both carotid arteries and the right vertebral artery were performed utilizing a power injector. Serial rapid films, in the frontal and lateral projections, were taken at a rate of 3/sec for 2 seconds followed by 1/sec for 4 seconds.

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TABLE I

Cerebrovascular Status of 15 Children After Repair of Coarctation of Aorta

	Patients		Cerebrovascular Anomaly
	no.	%	
Asymptomatic	11	73	None
Symptomatic (CNS symptoms)	4	27	Subclavian steal
Total	15	100	

CNS = central nervous system.

After cerebral arteriography, all patients underwent left heart catheterization. Pressures were measured as the catheter was withdrawn from the left ventricle to the descending aorta. In patients demonstrated to have subclavian steal on cerebral angiography, the systolic pressure gradient from the left subclavian artery to the descending aorta was measured. Arch aortography was performed in all patients.

Results

Eleven patients were asymptomatic (Table I). None of the 11 manifested cerebrovascular abnormalities, and no patient in the entire series had a berry aneurysm. Central nervous system symptoms developed in four patients postoperatively. All four of the patients had the subclavian steal syndrome. The findings in these four cases will be reported in detail.

Operative findings: Table II lists the operative findings and the surgical techniques used during the original operation in the four patients with the subclavian steal syndrome. Patient 1 had coarctation of the thoracic aorta that extended to involve the origin of the left subclavian artery. He also had hypoplasia of the aortic arch. Surgical correction was accomplished at age 13 years with use of prosthetic arterioplasty of the aorta and the left subclavian artery. Before correction, this patient had angiographically documented subclavian steal. Patient 2 had an interrupted aortic arch distal to the left subclavian artery associated with hypoplasia of the aortic isthmus. Surgical repair consisted of the Blalock-Park operation[3] (anastomosis of the end of the left subclavian artery to the descending aorta). In addition, the first branch of the left subclavian artery, thought to be the vertebral artery, was ligated. Patient 3 had isolated coarctation of the thoracic aorta. Resection of the coarctation with end to end anastomosis was performed at age 2.5 years. Patient 4 had an interrupted aortic arch distal to the left subclavian artery. Surgical repair was accomplished with prosthetic tube graft arterioplasty at age 12 years.

History and physical findings: The postoperative symptoms and clinical findings in the four symptomatic patients are summarized in Table III. The postoperative period ranged from 0.3 to 2 years. Patient 1 had exercise-induced hemianopsia lasting several minutes followed by severe headache. Patients 2 and 3 had dizziness and headache unresponsive to analgesic agents. Patient 4 had a major motor seizure followed by loss of consciousness 8 months postoperatively. The neurologic examination was normal in all patients, and studies performed to evaluate the seizure in Patient 4, including electroencephalogram and brain scan, revealed normal findings. The left arm pulse amplitude was decreased in all patients, and all had a systolic blood pressure differential of 20 mm Hg or more between the two arms. Two patients had a supraclavicular bruit.

Postoperative catheterization and angiography (Table IV): All patients were hypertensive. The residual gradient across the surgical anastomosis ranged from 20 to 50 mm Hg. A pressure gradient between the left subclavian artery and the

TABLE II

Operative Findings and Surgical Techniques Used at Original Operation in Four Patients with Postoperative Subclavian Steal

	Case 1	Case 2	Case 3	Case 4
Anatomic lesion	Coarctation of thoracic aorta involving the origin of LSA; hypoplasia of aortic isthmus	Interrupted aortic arch distal to LSA; hypoplasia of aortic isthmus	Coarctation of thoracic aorta	Interrupted aortic arch distal to LSA
Age at operation (yr)	13.0	6.0	2.5	12.0
Surgical technique	Prosthetic patch arterioplasty of aorta and LSA	Blalock-Park operation; ligation of first branch of LSA	Resection-re-anastomosis	Prosthetic tube graft interposition

LSA = left subclavian artery.

TABLE III

Postoperative Symptoms and Clinical Findings in Four Patients With Subclavian Steal

	Case 1	Case 2	Case 3	Case 4
CNS symptoms	Hemianopsia, exercise-induced	Recurrent headache and dizziness	Recurrent headache and dizziness	Seizure
Duration of symptoms (mo)	1 episode	9	12	1 episode
Left arm pulse amplitude	Decreased	Decreased	Decreased	Decreased
Systolic blood pressure differential between arms (mm Hg)	50	60	30	20
Supraclavicular bruit	Present	Present	Absent	Absent

TABLE IV

Postoperative Catheterization Data and Arch Aortographic Findings

	Case 1	Case 2	Case 3	Case 4
Age (yr) & sex	13.0 M	6.7 M	4.5 M	12.3 F
Years since operation	0.3	0.7	2.0	0.7
Systemic pressure (mm Hg)	140/80	155/70	130/75	135/90
Residual gradient across surgical repair (mm Hg)	50	45	30	20
Ascending aorta − LSA gradient (mm Hg)	50	20	NM	20
Proximal LSA obstruction	+	+	+	+
Retrograde filling of LVA and LSA	+	+	+	+

LSA = left subclavian artery, LVA = left vertebral artery; NM = not measured; + = present.

ascending aorta was demonstrated in three patients and could not be measured in the fourth. Selective right vertebral arteriography and arch aortography demonstrated retrograde filling of the left vertebral and left subclavian arteries and obstruction of the proximal subclavian artery in all patients (Fig. 1 and 2).

Surgery and results: Transcervical ligation of the left vertebral artery (Patients 1, 2 and 4) and aortic and left subclavian arterioplasty (Patient 3) resulted in complete disappearance of symptoms in all patients during a follow-up period of 11 to 20 months.

Discussion

Since Reivich and co-workers[4] drew attention to the reversal of flow in the vertebral artery resulting from proximal obstruction of the ipsilateral subclavian artery, many well documented cases of subclavian steal have been reported, particularly in adults. Symptomatic subclavian steal has been reported infrequently and seldom has been recognized in childhood.

From the physiologic standpoint, reduction of pressure in the subclavian artery by a stenosis or an obstructing lesion is the basic abnormality in subclavian steal. Flow in the ipsilateral vertebral artery reverses when pressure in the basilar artery exceeds that in the distal subclavian artery by 20 percent.[5] With reversal of flow in the vertebral artery, there is decreased flow to the cerebral tissue supplied by the vertebral-basilar system. Studies in man[6] and experimental animals[7] have shown a compensatory increase in anterograde flow in the carotid arteries and the contralateral vertebral artery. It appears that this increase does not sufficiently compensate for the retrograde vertebral flow on the affected side in patients with cerebral symptoms.

Symptomatology of subclavian steal: Subclavian steal can occur with or without symptoms, depending on the amount of blood siphoned from the brain. Most children with subclavian steal are asymptomatic, and the condition is usually discovered during angiographic

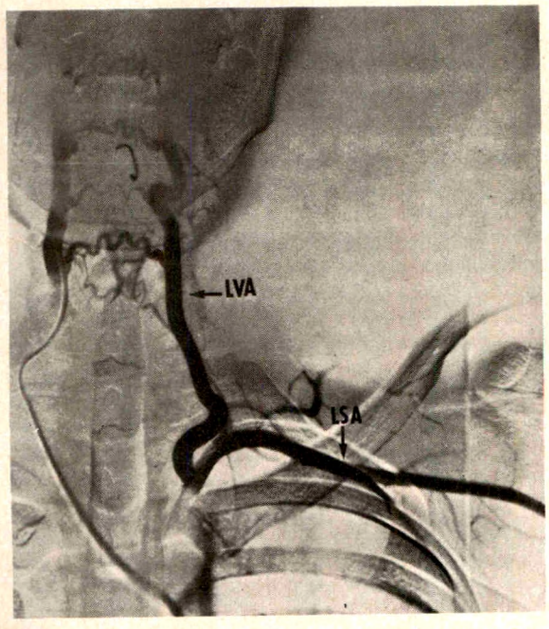

FIGURE 1. Patient 1. Selective right vertebral arteriogram in the frontal projection showing retrograde opacification of the left vertebral artery (LVA) and the left subclavian artery (LSA).

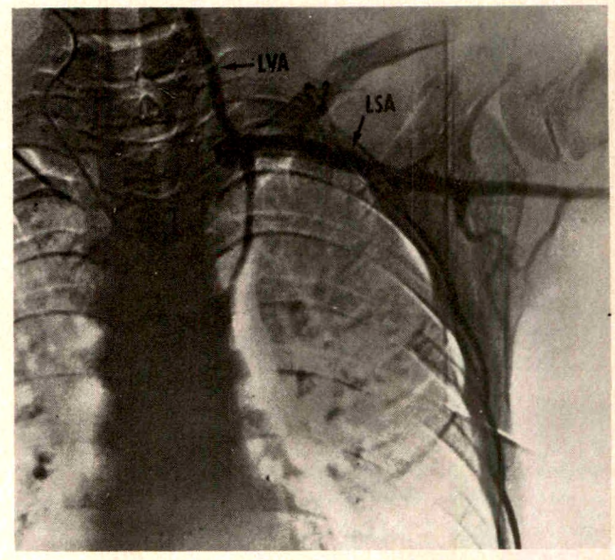

FIGURE 2. Patient 2. Selective right vertebral arteriogram in the frontal projection showing retrograde filling of the left vertebral (LVA) and the left subclavian artery (LSA). Note also opacification of the left internal mammary artery.

studies for congenital heart disease. The relative lack of symptoms in children when compared with findings in adults has been attributed to better collateral development and the absence of arteriosclerotic occlusive disease in children.[8] Symptoms were present in only 5 of 26 cases of angiographically documented congenital subclavian steal in children 11 years of age or older reviewed by Pieroni et al.[9] These were limited to pain and paresthesia of the arm, especially during exercise; no child had cerebral symptoms.

Subclavian steal leads to symptoms only when enough blood is diverted from structures perfused by the vertebral-basilar system,[10] that is, cerebellum, brain stem, occipital lobes, labyrinth, cochlea and upper spinal cord. As a consequence, signs and symptoms related to ischemia of these structures may be encountered; these include headache, dizziness, vertigo, arm pain and paresthesia, visual disturbances, ataxia and seizure.

Cerebral symptoms have not been seen in young children.[9] Our series is of interest because two of four patients were less than 10 years of age and all four patients had symptoms of vertebral-basilar insufficiency. To our knowledge this occurrence has not been previously documented in children with coarctation of the aorta. Folger and Shah,[11] in their study of 123 patients who had undergone Blalock-Taussig[12] anastomosis for tetralogy of Fallot, found 12 patients with subclavian steal, 7 of whom had symptoms suggestive of vertebral-basilar insufficiency. However, the significant degree of hypoxemia in these patients was thought to be a contributing factor in the development of their symptoms. The early appearance of cerebral symptoms in our patients demonstrates that development of collateral channels does not always compensate fully for the anatomic abnormality.[13]

Causes of subclavian arterial obstruction: Several conditions have been implicated in the development of significant obstruction of a subclavian artery. Although an arteriosclerotic plaque is the most common obstructive factor in the adult, it is uncommon in children. Two major categories of origin of subclavian steal predominate in children: congenital and acquired.

Congenital subclavian steal occurs when any congenital lesion prevents entrance of blood into the proximal subclavian artery at a pressure above that in the vertebral-basilar axis. Becker et al.[14] listed 55 potential anatomic lesions capable of producing subclavian steal. However, the majority of these lesions have not been reported in man. Case 1 in our series represents the congenital variety of subclavian steal. The majority of patients with a left aortic arch and congenital subclavian steal manifest hypoplasia, coarctation or complete interruption of the aortic arch with the subclavian artery arising distal to the obstruction.[9] The steal can be right- or left-sided, depending on the location of the subclavian artery and the site of obstruction. Congenital subclavian steal is more common with a right-sided aortic arch, and the underlying disease is usually hypoplasia, atresia or partial occlusion of an anomalous left subclavian artery.

The acquired form of subclavian steal in children is caused by stenosis of the proximal portion of the left subclavian artery after repair of coarctation and is produced by fibrosis, thrombosis or suture line distortion,[15] as in Patients 3 and 4 in our series. The left subclavian artery in these two patients was normal before the original operation. Acquired steal can also occur as a result of trauma to the subclavian artery[16,17] or of surgical procedures on the aortic arch and its great vessels. Ligation of the subclavian artery may be required during repair of a coarctation[18] and is necessary in the Blalock-Taussig anastomosis. Retrograde vertebral flow occurs unless flow to the distal subclavian artery is restored or the vertebral artery is ligated. In Patient 2 in our series, the first branch of the subclavian artery was ligated during the original operation, but this vessel was not the vertebral artery; possibly it was a cervical branch. Because the vertebral artery is not always the first branch of the subclavian artery, it must be carefully identified and ligated in surgical procedures using the subclavian artery.

Clinical and diagnostic features: Clinical signs of subclavian steal are readily detectable on physical examination. Diminished or absent radial pulse, a difference in blood pressure of at least 20 mm Hg between the two arms, and a supraclavicular bruit are the objective clinical findings in the classic case. The diagnosis of subclavian steal syndrome should be considered if the clinical signs of proximal subclavian obstruction are associated with symptoms of vertebral-basilar insufficiency. A helpful diagnostic aid is the appearance of neurologic symptoms when the involved arm is exercised[19]; these symptoms are caused by aggravation of the siphoning effect secondary to dilatation of the limb vascular bed.[5] Although arm exercise may precipitate symptoms of cerebral vascular insufficiency in patients with subclavian arterial obstruction, failure to do so does not rule out a steal. This test was positive in one of our patients (Case 1) and in only 9 of 93 adult patients reported in two large series by North[19] and Javid[20] and their co-workers.

Angiography, properly performed with the films correctly interpreted, is essential to establish an exact anatomic diagnosis. Arch aortography with serial late films may demonstrate retrograde vertebral and subclavian arterial flow on the affected side. This method is not infallible.[21] If the diagnosis of subclavian steal is strongly suspected, additional angiography is recommended. Selective injection of contrast material into the contralateral vertebral artery will demonstrate retrograde flow in the ipsilateral vertebral artery. The appearance of contrast material in the proximal one third of the ipsilateral vertebral artery or in the subclavian artery distal to its proximal obstruction implies retrograde flow and subclavian steal. Several authors[23–27] demonstrated retrograde opacification of the ipsilateral vertebral artery on contralateral vertebral arteriography in patients who were studied later and found to have no subclavian steal. The incidence rate of "false positive" steal in Cronquist's series[22] was as high as 20 percent in normal adult patients. In our series, none of the 11

asymptomatic patients had "false positive" steal on selective right vertebral arteriography. In our four symptomatic patients, reversed flow in the ipsilateral vertebral flow occurred after arch aortography as well as after contrast injection into the right vertebral artery.

Therapy: Recognition of the presence of subclavian steal is not sufficient indication for treatment. Surgery should not be recommended for the asymptomatic patient. Spontaneous recovery can occur in many patients, probably as a result of development of adequate collateral vessels.[24] Close observation with repeated and accurate interviews is recommended because abnormal neurologic symptoms of importance may be either unrecognized or misinterpreted.

In the presence of symptoms, treatment is directed toward restoring anterograde vertebral and subclavian arterial blood flow. Vascular repair with relief of subclavian arterial obstruction is recommended. If this is not feasible, ligation of the ipsilateral vertebral artery should relieve the symptoms of vertebral-basilar insufficiency.

References

1. **Haxton H:** The late results of excision of aortic coarctations. J Cardiovasc Surg 6:346–348, 1965
2. **Sedzimir CB, Jones EW, Hamilton D, et al:** Management of coarctation of the aorta and bleeding intracranial aneurysm in pediatric cases. Neuropaediatrie 4:124–133, 1973
3. **Blalock A, Park EA:** Surgical treatment of experimental coarctation (atresia) of the aorta. Ann Surg 119:445–456, 1944
4. **Reivich M, Holling HE, Roberts B, et al:** Reversal of blood flow through the vertebral artery and its effect on cerebral circulation. N Engl J Med 265:878–885, 1961
5. **Toole JF, McGraw CP:** The steal syndrome. Ann Rev Med 26: 321–329, 1975
6. **Hardesty WH, Whitacre WB, Toole JF, et al:** Studies on vertebral blood flow in man. Surg Gynecol Obstet 116:662–664, 1963
7. **Handa J, Ishikawa S, Huber P, et al:** Experimental production of "subclavian steal": electromagnetic flow measurements in monkey. Surgery 58:703–712, 1965
8. **Skalpe IO, Semb GS:** Collateral circulation in subclavian artresia. Scand J Thorac Cardiovasc Surg 3:207–210, 1969
9. **Pieroni DR, Brodsky ST, Row RD:** Congenital subclavian steal: report of a case occurring in a neonate and review of the literature. Am Heart J 84:801–807, 1972
10. **Piccone VA, LeVeen HH:** The subclavian steal syndrome. Ann Thorac Surg 9:51–75, 1970
11. **Folger GM, Shah KD:** Subclavian steal in patients with Blalock-Taussig anastomosis. Circulation, 31:241–248, 1965
12. **Blalock A, Taussig HB:** The surgical treatment of malformations of the heart in which there is pulmonary stenosis or pulmonary atresia. JAMA 128:189–202, 1945
13. **Borushok MJ, White RI Jr, Oh KS, et al:** Congenital subclavian steal. Am J Roentgenol Radium Ther Nucl Med 121:559–564, 1974
14. **Becker AE, Becker MJ, Edwards JE:** Congenital anatomic potentials for subclavian steal. Chest 60:4–13, 1971
15. **Johnson TE:** Angiography in the general practice of radiology. Radiology 81:38–46, 1963
16. **Rojas RH, Levitsky S, Stansel HC:** Acute traumatic subclavian steal syndrome. J Thorac Cardiovasc Surg 51:113–115, 1966
17. **Shumaker HB:** Use of subclavian artery in surgical treatment of coarctation of the aorta. Surg Gynec Obstet 93:491–495, 1951
18. **Fields WS, Lemak NA:** Joint study of extracranial arterial occlusion. VIII. Subclavian steal—a review of 168 cases. JAMA 222: 1139–1143, 1972
19. **North RR, Fields WS, DeBakey ME:** Brachial-basilar insufficiency syndrome. Neurology 12:810–820, 1962
20. **Javid H, Julian OC, Dye WS, et al:** Management of cerebral arterial insufficiency caused by reversal of flow. AMA Arch Surg 90: 634–643, 1965
21. **McMullan MH, Hardy JD:** Lesions of the subclavian artery. Survey of 31 cases with emphasis on steal syndrome. Ann Surg 178: 80–86, 1972
22. **Cronquist S:** Vertebral catheterization via femoral artery. Acta Radiol 55:113–118, 1961
23. **Couves CM, Hilliard JR, Pribram HFW:** Abnormalities of the vertero-basilar circulation due to subclavian artery disease. Can Med Assoc J 88:343–346, 1963
24. **Gorman JF, Navarri JR, McLean H:** Subclavian steal syndrome. Arch Surg 88:350–353, 1964
25. **Swann GF:** Vertebral arteriography using the Sheldon needle and modification of it. Br J Radiol 31:23–34, 1958
26. **Gonzales L, Weintraub RA, Wiot JF, et al:** Retrograde vertebral artery flow: a normal phenomenon. Radiology 82:211–216, 1964
27. **Heyman A, Young WG Jr, Dillon M, et al:** Cerebral ischemia caused by occlusive lesions of the subclavian or innominate arteries. AMA Arch Neurol 10:581–584, 1964

Congenital Aortic Stenosis Secondary to Dysplasia of Congenital Bicuspid Aortic Valves Without Commissural Fusion

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The hearts of nine children with clinical evidence of congenital valve stenosis and a congenital bicuspid aortic valve were reviewed. Aortic stenosis was diagnosed on the basis of cardiac catheterization data in four patients, operative findings in two and auscultatory findings in three. The patients were 1 month to 9 years old; six were male and three female. In each patient the two commissures of the valve were free to the aortic wall. The cusps were thickened, rolled and redundant; microscopic studies revealed that they consisted of immature loose connective tissue consistent with a dysplastic or incompletely differentiated valve. The valve orifice was obstructed by the dysplastic cusps, and dysplastic changes rather than the commissural fusion were responsible for the observed aortic stenosis. These valves do not appear amenable to valvotomy because obstruction is due to the abnormal valve tissue. These findings may explain the occasional poor results of valvotomy in infants and children with congenital aortic valve stenosis.

Congenital aortic stenosis is an uncommon anomaly with an estimated incidence rate of 3 to 6 percent of all cases of congenital heart disease.[1,2] The anomaly includes cases of aortic valve stenosis, supravalve stenosis, subaortic stenosis and hypoplasia of the aortic valve ring. In approximately 70 percent of patients stenosis is secondary to deformity of the aortic valve. This congenitally stenotic valve has been repeatedly described in clinical reports as a bicuspid valve with fusion of one commissure[3–5] and in autopsy review as a unicommissural or acommissural valve.[6–8]

The most common congenital cardiac anomaly is a bicuspid aortic valve, estimated to be present in 2 percent of the population.[9] The congenital bicuspid aortic valve is not inherently stenotic[10]; although it frequently becomes stenotic in later life,[9,11] such stenosis is secondary to fibrosis and calcification of the cusps and not to fusion of the commissures.[11] In this study we attempted to determine if the congenital bicuspid aortic valve is responsible for some cases of congenital aortic valve stenosis and to assess the status of the valve commissures in patients with this condition.

Material and Methods

Selection of cases: The files of the Armed Forces Institute of Pathology were searched for all patients under age 20 years with aortic stenosis and a bicuspid aortic valve. Only cases with complete autopsy protocols and clinical summaries and in which the heart was available for review were included in this study. The aortic valve was evaluated using the criteria outlined by Roberts[9] to distinguish between acquired and congenital bicuspid valves. By these criteria the circumferential distances between the two commissures in the congenital bicuspid valve are equal or nearly equal around the aortic ring, and the margins of the commissures against the aortic wall are on the same horizontal level (Fig. 1). A raphe may be present in one of the cusps, but the margin of the raphe against the aortic

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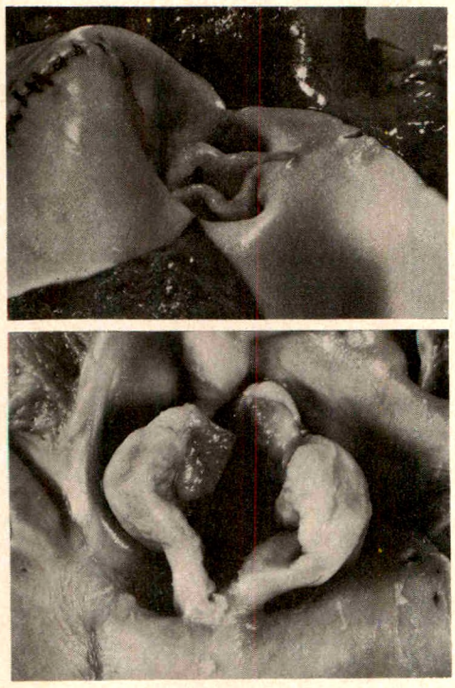

FIGURE 1. Photograph of dysplastic bicuspid aortic valves viewed from the aorta. There are two well formed commissures that are free to the aortic wall. The valve orifice is narrowed and obstructed by the thick redundant valve cusps.

FIGURE 2. Photograph of histologically normally differentiated bicuspid aortic valve with two well formed free commissures and a raphe **(arrow).** The cusps are so translucent that the sinuses of Valsalva had to be filled with cotton to photograph the valve.

wall is below the horizontal plane of the attachments of the commissures and the raphe does not extend to the free margin of the cusp (Fig. 2). The fused commissure of the acquired bicuspid valve is easily distinguished from a raphe. In valves with a fused commissure the circumference of attachment of the fused cusp to the aortic wall is nearly twice that of the nonfused cusp, the plane of attachment of the fused commissure against the aortic valve is on the level of the nonfused commissure and the fused commissure extends to the free margin of the valve cusp.

Only patients with a congenital bicuspid aortic valve and clinical evidence of aortic stenosis were included in this study. Patients with clinical evidence of aortic stenosis who had a dome-shaped (acommissural), unicuspid or tricuspid aortic valve were excluded, as were patients with the hypoplastic left heart syndrome.

Protocol: The gross appearance of the aortic valve cusps was examined in each heart, and both commissures were assessed for evidence of commissural fusion. In all cases the thickness of the left and right ventricles at the level of the tip of the papillary muscles and the relative size of the aortic and pulmonary valve rings were measured and the presence and type of accompanying cardiac abnormalities noted. Data on heart weight were obtained from autopsy protocols.

The clinical records, including cardiac catheterization reports, operative reports and clinical narrative summaries, were searched for evidence of aortic stenosis. The following evidence was accepted as indicative of aortic stenosis: (1) the presence of a systolic pressure gradient greater than 50 mm Hg across the aortic valve at cardiac catheterization; (2) evidence of aortic stenosis described by the surgeon at the time of open valvotomy; and (3) findings during life of a typical systolic ejection murmur with congestive heart failure not otherwise explained, together with autopsy findings of definite and otherwise unexplained left ventricular hypertrophy.

An age-matched control group of patients less than 20 years old with a congenital bicuspid aortic valve but without clinical

TABLE I

Clinical Findings in Nine Patients With a Dysplastic Bicuspid Aortic Valve

Case no.	Sex	Age	Grade of Systolic Murmur	AS	CHF	Syncope	Exertional Intolerance	Gradient Across Aortic Valve (mm Hg)	Aortic Valve Surgery	Cause of Death
1	F	9 yr	5/6	+	0	0	0	100	+	Postop
2	M	5 yr, 9 mo	6/6	+	0	+	+	. . .	+	Postop
3	M	4 1/2 yr	"Loud"	+	0	+	+	80	+	Postop
4	F	4 yr, 6 mo	4/6	+	+	+	+	70	+	Postop
5	F	4 1/2 mo	3/6	+	+	0	0	. . .	0	CHF
6	M	4 mo	4/6	+	+	0	0	. . .	+	Postop
7	M	4 mo	4/6	+	0	0	0	60	+	Postop
8	M	6 wk	3/6	+	+	0	0	. . .	0	Aspiration
9	M	5 wk	3/6	+	+	0	0	. . .	0	CHF

AS = clinical diagnosis of aortic stenosis; CHF = congestive heart failure; Postop = postoperative; + = present; 0 = absent; . . . = not assessed.

evidence of aortic stenosis was selected from the files of the Armed Forces Institute of Pathology. The hearts of these patients were examined in the manner described and the clinical records studied for evidence of aortic stenosis.

Histology: Sections were taken through the bicuspid aortic valve leaflets of the hearts in both patient groups. The tissue blocks were refixed in 10 percent neutral buffered (pH 7.0) formalin and processed for paraffin embedding. Sections were stained with hematoxylin-eosin, the Movat pentachrome stain, colloidal iron and Verhoff's elastic stain.

Results

Clinical features (Table I): Nine children were found with clinical evidence of aortic stenosis and a

TABLE II

Anatomic Findings in Nine Patients With a Dysplastic Bicuspid Aortic Valve

Case no.	Heart Weight (normal ± SD)*	LV (cm)	RV (cm)	Circumference: Ao Valve Ring (cm)	Circumference: Pulmonary Valve Ring (cm)	Dysplasia: Ao Valve	Dysplasia: Mitral Valve	Myocardial Fibrosis	Other Cardiac Findings
1	250 (129 ± 19)	1.3	0.3	5.5	5.5	+	0	Acute infarct	Coarct, repaired
2	300 (105 ± 14)	2.0	0.5	3.0	3.0	+	+, mild	0	Coarct., mild
3	. . . (84 ± 12)	1.4	0.4	Equal†		+	0	+	0
4	175 (104 ± 6)	1.3	0.3	3.6	3.6	+	0	0	Coarct., mild
5	83 (33 ± 6)	1.4	0.3	3.0	3.0	+	+, mild	0	0
6	75 (31 ± 7)	1.2	0.4	3.0	3.0	+	0	±	0
7	60 (31 ± 7)	1.5	0.4	2.5	2.5	+	+, mild	+ Subendocardial	0
8	. . . (25 ± 7)	1.6	0.5	Equal†		+	0	0	0
9	65 (24 ± 7)	1.6	0.5	2.0	2.5	+	0	+	0

* Data from Schultz and Giordano.[12]
† Aortic pulmonary valve rings said to be "equal"; no measurements given.
Ao = aortic; Coarct. = coarctation of aorta;
LV = thickness of the left ventricular posterior wall at the level of the tip of the papillary muscles; RV = thickness of the right ventricular anterior wall at the level of the tip of the papillary muscles; SD = standard deviation; + present; 0 absent; = . . . not assessed.

TABLE III

Clinical and Anatomic Findings in 12 Patients With a Normally Differentiated Bicuspid Aortic Valve

Case no.	Sex	Age	Heart Weight (Normal ± SD)* (g)	LV (cm)	RV (cm)	Circumference: Ao Valve Ring (cm)	Circumference: Pulmonary Valve Ring (cm)	Valve Dysplasia	Associated Cardiac Findings	Clinical Diagnosis
1	M	9 yr	225 (138 ± 12)	1.2	0.6	5.2	5.5	0	Coarct., VSD	Coarct., attempted surgical repair
2	F	2 yr	126 (58 ± 11)	1.0	0.8	4.0	4.0	0	Coarct., VSD	Coarct., attempted surgical repair
3	M	9 mo	95 (45 ± 7)	1.0	0.3	3.5	3.8	0	Coarct.	Choledochal cyst attempted surgical repair
4	M	6 mo	83 (40 ± 8)	1.0	0.5	2.5	2.6	0	Coarct., PDA	Mongolism
5	M	3 mo	75 (30 ± 7)	0.8	0.6	2.2	2.2	0	Coarct., PDA	Coarct.
6	F	3 mo	. . . (28 ± 4)	1.0	0.5	2.2	2.5	0	Coarct.	Coarct.
7	M	2 mo	90 (27 ± 7)	1.2	0.5	3.0	3.2	0	Coarct.	Sudden death
8	M	2 mo	65 (27 ± 7)	0.8	0.3	2.8	3.2	0	Coarct.	Coarct.
9	M	2 mo	79 (27 ± 7)	0.8	0.4	3.8	4.0	0	Coarct., PDA, ASD	Coarct.
10	M	7 wk	68 (26 ± 7)	0.8	0.4	2.2	2.5	0	Coarct., PDA, ASD	Idiopathic cardiac hypertrophy
11	M	7 wk	. . . (26 ± 7)	0.8	0.8	2.8	3.0	0	Coarct., PDA, ASD	Coarct.
12	F	5 wk	46 (24 ± 7)	0.6	0.3	2.2	2.5	0	Coarct., PDA, ASD	Congenital heart disease

* Data from Schultz and Giordano.[12]
Ao = aortic; ASD = atrial septal defect; Coarct. = coarctation of aorta; LV = thickness of the left ventricular posterior wall at the level of the tip of the papillary muscles; PDA = patent ductus arteriosus; RV = thickness of the right ventricular anterior wall at the level of the tip of the papillary muscles; SD = standard deviation; VSD = ventricular septal defect; + = present; 0 = absent; . . . = not assessed.

congenital bicuspid aortic valve. They ranged in age from 1 month to 9 years (average 2.8 years) and could be classified into two age groups: age 6 weeks to 5 months (five children) and age 4 1/2 to 9 years (four children). The clinical evidence for aortic stenosis was based on (1) a systolic pressure gradient across the aortic valve demonstrated at cardiac catheterization (four patients); (2) surgical evaluation of the valve at the time of attempted valvotomy without prior catheterization (two patients); or (3) the presence of a typical systolic ejection murmur of aortic stenosis with well described congestive heart failure and left ventricular hypertrophy at autopsy with no other explanation (three patients). A loud systolic ejection murmur was described in each patient and congestive heart failure was present in five patients. Exertional syncope occurred in one patient.

Aortic valvotomy was attempted in six patients; three died during or immediately after the operation, and three died within days of the intervention. The latter three experienced bradycardia, hypotension and cyanosis within 24 hours of the surgical procedure and, despite vigorous medical treatment, all were dead within 5 days of the operation.

Anatomic findings (Table II): The cusps of the aortic valve were thickened, rolled and redundant in all nine patients. The effective orifice of the aortic valve appeared compromised by the redundant valve cusps (Fig. 1); however, both commissures were free to the aortic wall, and there was no evidence of any fusion of the commissures. The left ventricle was hypertrophied and the heart was heavier than normal for age in all patients. The heart weight in seven hearts for which data on weight were available was 2.6 times the normal value.[12] Five of the nine patients had evidence of myocardial fibrosis. The aortic and pulmonary valve rings were almost equal in circumference in all cases; hypoplasia of the aortic valve ring therefore seems an unlikely cause of the aortic stenosis in these patients. Three patients had a mildly dysplastic mitral valve. A coarctation of the aorta had been repaired in Patient 1 and a mild coarctation of the aorta was present in two other patients.

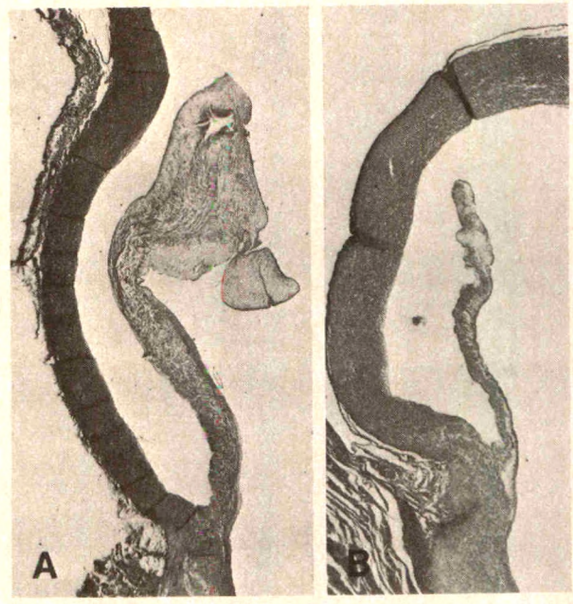

FIGURE 3. Dysplastic **(A)** and normal **(B)** bicuspid aortic valves in cross section. The distal portion of the dysplastic valve is thickened and redundant. The dysplastic changes may be focal, as pictured; however, more frequently the entire valve is involved in patients with congenital aortic valve stenosis. (Movat pentachrome stain ×8.)

Control group (Table III): The 12 age-matched control patients had no clinical or autopsy evidence of

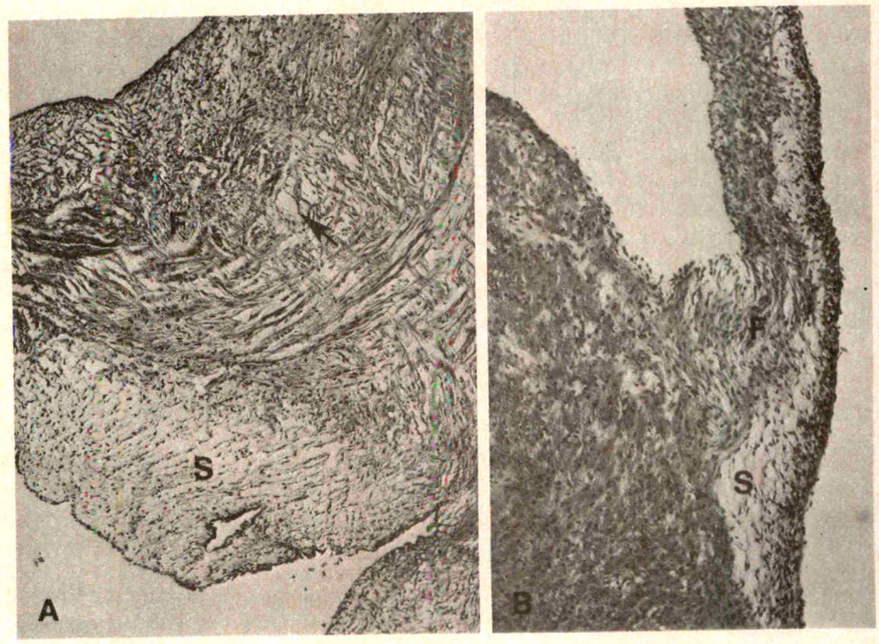

FIGURE 4. Microscopic view from the base of a dysplastic **(A)** and histologically normal **(B)** bicuspid aortic valve. In **B,** the fibrosa (F), spongiosa (S) and ventricularis (V) are clearly distinguished. The base of the dysplastic valve **(A)** is markedly thickened. The ventricularis appears completely replaced by the spongiosa, which also encroaches **(arrow)** on the fibrosa. The collagen bundles of the fibrosa appear disoriented and fragmented. (Movat pentachrome stain ×80 **[A]** and ×100 **[B],** both reduced by 15 percent.)

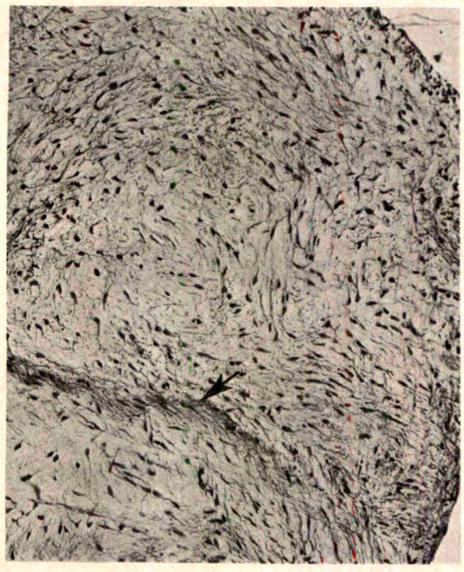

FIGURE 5. The spongiosa of the dysplastic valve is quite cellular and is composed primarily of small spindle cells resembling fibroblasts set in an acid mucopolysaccharide matrix and haphazardly arranged bundles of collagen **(arrow).** (Movat pentachrome stain ×130, reduced by 15 percent.)

aortic stenosis, although all 12 had a congenital bicuspid aortic valve. They ranged in age from 5 weeks to 9 years (average 1.1 years). All 12 had severe coarctation of the aorta, and the death of 11 was apparently directly related to the coarctation. Two patients also had a ventricular septal defect, and six, all under age 6 months, had a patent ductus arteriosus or atrial septal defect, or both.

Histology: Microscopically, the cusps of the aortic valves in the nine children with clinical evidence of aortic stenosis were markedly thickened. There was distortion of the architecture[13] by comparison with the normal bicuspid aortic valve of children in the control group (Fig. 3 and 4). The thickened cusps consisted of a basophilic staining mucopolysaccharide matrix within which were embedded fibroblasts and randomly oriented bundles of collagen (Fig. 5). This loose connective tissue, which resembles the normal spongiosa of the aortic valve cusps, encroached upon and replaced the ventricularis and fibrosa of the valve cusps. The majority of the cusps consisted entirely of this loose connective tissue; however, remnants of the ventricularis and fibrosa interrupted by accumulations of abnormal loose connective tissue were often found at the base of the cusps. There were no foci of calcification in the nine dysplastic valves.

Discussion

Although it is well recognized that the congenital biscuspid aortic valve is not inherently stenotic,[9–11] some authors[3–5] have suggested that, when congenital aortic stenosis occurs with a bicuspid aortic valve, obstruction is secondary to fusion of a valve commissure. In our study all nine patients with clinical evidence of aortic stenosis had a bicuspid aortic valve and nonfused (free) commissures. In each patient the aortic stenosis was secondary to obstruction of the valve orifice by the thickened redundant cusps of the dysplastic or incompletely differentiated valve. The valve rings were not hypoplastic and therefore not responsible for the narrowing of the valve orifice. We were unable to find one example of a bicuspid valve with a fused commisure in our cases of congenital aortic valve stenosis.

Dysplastic semilunar valves: Valve dysplasia in the absence of commissural fusion has been reported as a cause of congenital stenosis of both the pulmonary valve[14] and the tricuspid aortic valve.[15] Other reports of congenital aortic stenosis[16–18] have described marked thickening and nodularity of the stenotic aortic valve. Such changes have been observed in valves with one, two or three distinct cusps, as well as in valves with only partially differentiated cusps (acommissural or dome-shaped aortic valves). Although these changes are neither illustrated nor described in detail in these reports,[16–18] it is probable that they represent examples of valve dysplasia. In our experience (unpublished observations) the dysplastic aortic valve may be unicuspid, bicuspid or tricuspid, as well as dome-shaped.

A dysplastic stenotic pulmonary valve is frequently present in patients with Noonan's syndrome.[14,19,20] The stenotic valve is usually tricuspid[14,19] and stenosis is secondary to the marked thickening of the individual cusps. In these patients the absence of a pulmonary ejection click[6,19] is considered suggestive of pulmonary stenosis secondary to a dysplastic pulmonary valve. Other distinctive angiographic, electrocardiographic and echocardiographic findings may also be present.[21,22] Our nine patients with a dysplastic aortic valve and stenosis had no distinctive clinical, electrocardiographic, roentgenographic or angiocardiographic findings to distinguish them from patients with other forms of congenital aortic valve stenosis.

The abnormal valve tissue of the dysplastic or incompletely differentiated valve[14,23,24] resembles embryonic connective tissue and is similar to the connective tissue of the cardiac valves in 8 to 12 week old fetuses—hence, the terms dysplasia[14,15] or incomplete differentiation.[23] Dysplasia implies abnormal development rather than failure to mature or develop and is perhaps a more appropriate term because fetal valves, although composed largely of loose connective tissue, are not deformed. Valve dysplasia may affect any of the cardiac valves, although in large autopsy series the aortic valve is most frequently involved[23] and 25 percent of patients have multiple valve involvement.[24] The dysplastic changes may be so severe and extensive that the entire valve is distorted, as in all our nine patients, or mild and focal without evidence of impairment of valve function.

In reviewing specimens for this study, we occasionally observed mild degrees of dysplasia of the aortic valve in patients who died of other types of congenital heart disease without clinically apparent aortic stenosis. The fate of such valves is unknown.[25] It is possible that differentiation to normal continues or that these valves form the basis for further fibrosis and calcification, which is one cause of calcific aortic stenosis in patients over 40 years of age.[11,26]

Significance of bicuspid aortic valve: It has been estimated that in 45 percent of adults with isolated aortic stenosis, stenosis is secondary to a congenital bicuspid aortic valve. In our review[11] of 152 patients over age 20 years with a bicuspid aortic valve, we found none with dysplastic changes in the valve cusps. Aortic stenosis was present in 28 percent of these patients, increasing in incidence after age 40 years. Stenosis was always secondary to fibrosis and calcification of the valve cusps rather than to commissural fusion, and only eight patients manifested commissural fusion of even mild degree.

Surgical implications: In the majority of infants and children with isolated congenital aortic valve stenosis, the aortic valve is either acommissural (dome-shaped) or unicommissural.[6,7] The exact incidence rate of these two forms of valve deformities in congenital aortic valve stenosis is not known, but it has been reported as high as 80 percent.[6] The unicommissural valve has frequently been mistaken for a bicuspid aortic valve with commissural fusion. This has led many authors[3–5] to consider aortic valvulotomy the preferred treatment of congenital aortic stenosis, presumably performing the operation to open the fused commissure of a bicuspid aortic valve. Unicommissural valves are amenable to aortic valvulotomy, but anatomically they are not bicuspid aortic valves with fused commissures.

Clinically, especially at the time of surgery, it is extremely important to distinguish the dysplastic bicuspid or tricuspid aortic valve with normal commissures from the unicommissural or acommissural aortic valve.[6] Because aortic stenosis in patients with a dysplastic bicuspid aortic valve is secondary to the thickened redundant aortic cusps rather than to commissural fusion or absence of commissures, valvotomy probably offers little hope for relief in these patients. Indeed, in three of our cases in which valvotomy was attempted, death occurred during or shortly after operation. At necropsy the incision was found to be either extremely minute, offering no further increase in valve opening, or made through a cusp next to a commissure, producing a markedly insufficient valve that would be tolerated poorly by a patient postoperatively.

Several recent reports[26–28] presenting the results of valvotomy in children with congenital aortic valve stenosis have described poor results in a significant number of patients and mortality rates ranging from 33 to 85 percent. Detailed morphologic descriptions of the aortic valves in these children with congenital aortic stenosis are not available; however, many of the valves were described as primitive in nature[25] or thickened and redundant.[26,27] These descriptions of stenotic aortic valves are suggestive of dysplastic and possibly bicuspid aortic valves.

References

1. **Keith JD, Rowe RD, Vlad P:** Heart Disease in Infancy and Childhood. New York, Macmillan, 1967, p 247–290
2. **Hoffman JIE:** The natural history of congenital isolated pulmonic and aortic stenosis. Ann Rev Med 20:15–21, 1969
3. **Morrow AG, Goldblatt A, Braunwald E:** Congenital aortic stenosis II. Surgical treatment and the results of operation. Circulation 27:450–462, 1963
4. **Ellis FH, Kirklin JW:** Congenital valvular aortic stenosis: anatomic findings and surgical technique. J Thorac Cardiovasc Surg 43: 199–202, 1962
5. **Simon AL, Reis RL:** The angiographic features of bicuspid and unicommissural aortic stenosis. Am J Cardiol 28:353–358, 1971
6. **Moller JH, Nakib A, Eliot RS, et al:** Symptomatic congenital aortic stenosis in the first year of life. J Pediatr 69:728–734, 1966
7. **Edwards JE, Carey LS, Neufield HN, et al:** Congenital Heart Disease: Correlation of Pathologic Anatomy and Angiocardiography. Philadelphia, WB Saunders, 1965, p 706–722
8. **Roberts WC:** Valvular, subvalvular and supravalvular aortic stenosis: morphologic features. Cardiovasc Clin 5:97–126, 1973
9. **Roberts WC:** The congenitally bicuspid aortic valve: a study of 85 autopsy cases. Am J Cardiol 26:72–82, 1970
10. **Edwards JE:** The congenital bicuspid aortic valve. Circulation 23:485–488, 1961
11. **Fenoglio JJ, McAllister, HA, DeCastro CM, et al:** The congenital bicuspid aortic valve after age 20. Am J Cardiol 39:164–169, 1977
12. **Schulz DM, Giordano DA:** Hearts of infants and children. Arch Pathol 74:464–471, 1962
13. **Gross L, Kugel MA:** Topographic anatomy and histology of the valves in the human heart. Am J Pathol 7:445–474, 1931
14. **Koretzky ED, Moller JH, Korns ME, et al:** Congenital pulmonary stenosis resulting from dysplasia of the valve. Circulation 40:43–53, 1969
15. **Davis GI, McAllister WH, Friedenberg MJ:** Congenital aortic stenosis due to failure of histogenesis of the aortic valve (myxoid dysplasia). Am J Roentgenol 95:621–628, 1965
16. **Gasul BM, Arcilla RA, Lev M:** Heart Disease in Children: Diagnosis and Treatment. Philadelphia, JB Lippincott, 1966, p 807–815.
17. **Spencer FC, Neill CA, Sank L, et al:** Anatomical variations in 46 patients with congenital aortic stenosis. Am Surg 26:204–215, 1960
18. **Hastreiter AR, Oshima M, Milier RA, et al:** Congenital aortic stenosis syndrome in infancy. Circulation 28: 1084–1095, 1963
19. **Linde LM, Turner SW, Sparkes RS:** Pulmonary valvular dysplasia: a cardiofacial syndrome. Br Heart J 35:301–304, 1973
20. **Nora H, Nora AH, Sinha AK, et al:** The Ulrich-Noonan syndrome (Turner phenotype). Am J Dis Child 127:48–55, 1974
21. **Ehler KH, Engle MA, Leon AR, et al:** Eccentric ventricular hypertrophy in familial and sporadic instances of 46 XX, XY Turner pheonotype. Circulation 45:639–652, 1972
22. **Nora JJ, Lortscher RH, Spangler RD:** Echocardiographic studies of left ventricular disease in Ulrich-Noonan syndrome. Am J Dis Child 129:1417–1420, 1975
23. **Hyams VJ, Manion WC:** Incomplete differentiation of the cardiac valves. Am Heart J 76: 173–182, 1968
24. **Bharati S, Lev M:** Congenital polyvalvular disease. Circulation 47:575–586, 1973
25. **Cohen LS, Friedman WF, Braunwald E:** Natural history of mild congenital aortic stenosis elucidated by serial hemodynamic studies. Am J Cardiol 30:1–5, 1972
26. **Roberts WC:** The structure of the aortic valve in clinically isolated aortic stenosis. An autopsy study of 162 patients over 15 years of age. Circulation 42:91–97, 1970
27. **Coran AG, Bernhard WF:** The surgical management of valvular aortic stenosis during infancy. J Thorac Cardiovasc Surg 58: 401–408, 1969
28. **Bernhard WF, Keane JF, Fellows KE, et al:** Progress and problems in the surgical management of congenital aortic stenosis. J Thorac Cardiovasc Surg 66:404–419, 1973
29. **Lakier JB, Lewis AB, Heymann MA, et al:** Isolated aortic stenosis in the neonate: natural history and hemodynamic considerations. Circulation 50:801–808, 1974

Echocardiographic Features of Total Anomalous Pulmonary Venous Drainage Into the Coronary Sinus

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Echocardiograms were obtained from five infants with total anomalous pulmonary venous drainage to the coronary sinus or the portal system or the superior vena cava and from one child with a secundum atrial septal defect and a large coronary sinus due to persistence of the left superior vena cava. The results demonstrate that an enlarged coronary sinus is positioned consistently posterior to the left atrium in approximately the same horizontal plane as the aortic valve. Echocardiographically the coronary sinus can be located as an echo complex behind the left atrium by using the aortic root as a reference point. The echo complex can be differentiated from the other spurious echoes in the left atrium by its characteristic phasic motions. The additional demonstration of the enlarged common pulmonary venous chamber behind the right atrium confirms the diagnosis of anomalous pulmonary venous drainage to the coronary sinus. For other types of anomalous pulmonary venous return, anatomic diagnosis with single crystal M mode echocardiography is not always possible because of the positional variability of the common pulmonary venous chamber in relation to the left atrium.

Echocardiography may be helpful in establishing the diagnosis of total anomalous pulmonary venous drainage. Indirect signs such as right ventricular volume overload, due to an enlarged right ventricle and paradoxic intraventricular septal motion,[1,2] and a small left atrium[3] can be suggestive of this lesion. Recently, visualization of the common pulmonary venous chamber as an echo-free space posterior to the left atrium and bounded anteriorly by an anomalous linear echo complex has been reported[4] as a diagnostic anatomic feature of total anomalous pulmonary venous drainage to various segments of the systemic venous system. However, the diagnostic echocardiographic features distinguishing different types of total anomalous pulmonary venous drainage and the diagnostic difficulties of using single crystal M mode echocardiography have not been fully considered. This study presents observations on five consecutive infants with total anomalous pulmonary venous drainage to various parts of the systemic venous circuit, describes the characteristic features of total anomalous pulmonary venous return to the coronary sinus and discusses the reasons for the diagnostic difficulties we and others have encountered when using single crystal echocardiography in evaluating the supra- and infracardiac types of anomalous pulmonary venous drainage.

Material and Methods

Patients: Five infants (Table I), aged 15 hours to 39 months, with total anomalous pulmonary venous drainage to (1) the coronary sinus (three infants), (2) the portal system (one infant), or (3) the superior vena cava (one infant) were studied. In addition, an infant with a secundum atrial septal defect and a large coronary sinus due to persistence of the left superior vena cava was studied. Echocardiograms were performed on the same day as cardiac catheterization.

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TABLE I

Preoperative Hemodynamic and Echocardiographic Data of Five Patients With Total Anomalous Pulmonary Venous Drainage

	Case 1	Case 2	Case 3	Case 4	Case 5
Age	4 mo	2 mo	36 hr	15 hr	39 mo
BSA (m^2)	0.25	0.18	0.21	0.24	0.49
Site of PVD	CS	CS	CS	Infra-diaphragmatic	LSVC
PAP (mm Hg)	65/20 (45)	55/20 (30)	55/9 (24)	80/40 (60)	39/12 (23)
APD					
RV					
cm	2.0	2.3	1.2	1.4	2.7
cm/m^2	8.0	12.7	5.7	5.8	5.5
LV (cm)	0.85	0.75	0.90	0.90	2.00
RV/LV (%)	143	179	100	116	108
LA/AO (%)	0.68	0.58	0.76	0.86	1.00
IVS motion	Parad.	Parad.	Parad.	Parad.	Parad.
CPVC echo localization	AVJ and dorsal to RA	AVJ and dorsal to RA	AVJ and dorsal to RA	ND	Dorsal to RA
Pulmonary valve					
PEP (msec)	66	68	40	75	48
RVET (msec)	204	155	195	185	360
PEP/RVET	0.32	0.44	0.21	0.41	0.13
RVDWT (cm)	0.4	0.6	0.5	0.5	1.1

Figures in parentheses indicate mean pressures.
AO = aorta; APD = anteroposterior dimension; AVJ = atrioventricular junction; BSA = body surface area; CPVC = common pulmonary venous chamber; CS = coronary sinus; IVS = interventricular septum; LA = left atrium; LSVC = left superior vena cava; LV = left ventricle; ND = not determined; PAP = pulmonary arterial pressure; Parad. = paradoxic; PEP = preejection period; PVD = pulmonary venous drainage; RA = right atrium; RV = right ventricle; RVDWT = right ventricular diastolic wall thickness; RVET = right ventricular ejection time.

The hemodynamic, angiographic and operative findings established the anatomic diagnosis in all infants.

Echocardiographic procedures: Postoperative echocardiograms were available in all. Echocardiograms were obtained using a focused 5 or 3.5 megahertz transducer, positioned at the second to fourth intercostal space, with a Smith-Kline echocardiograph interfaced with a Honeywell 1856 strip chart recorder. The left atrium was explored distally and proximally to the level of the aortic root by recording from both high (second left interspace) and low (fourth interspace) parasternal positions. The atrioventricular (A-V) junction was viewed using multiple scans from the aorta to the left ventricle and varying the transducer angulation along the leftward-superior and leftward-inferior direction as well as along the long axis of the left ventricle. The right atrium was scanned by angulating the transducer to the right and superiorly from a lower left sternal position so that the right atrium would be visualized superior to the septal leaflet of the tricuspid valve. Technically satisfactory echocardiograms were obtained in all infants.

The coronary sinus was visualized echocardiographically during cardiac catheterization in two infants, one with an enlarged coronary sinus due to persistent left superior vena cava and the other with total anomalous pulmonary venous return to the coronary sinus, by injecting 2 to 3 ml of 5 percent dextrose in water into the left superior vena cava and the left atrium, respectively.

Measurements: The right ventricular end-diastolic anterior wall thickness and anteroposterior dimensions were measured at the time of the R wave peak of the electrocardiogram. The right ventricular dimensions were indexed to body surface area[5] and were also expressed as a ratio between the right and left ventricles. The left ventricular end-diastolic dimensions were measured at the level of maximal mitral valve amplitude at the time of R wave peak.[6]

The preejection period and the ejection time of the right ventricular systole were measured from the pulmonary valve echo, and the results expressed as a ratio.[7] The anteroposterior dimensions of the left atrium and aorta were measured at end-systole and also expressed as a ratio.[8]

Pathologic material: The positional variability of the common pulmonary venous chamber in relation to the left atrium and the aortic root was studied in 20 postmortem heart specimens from patients with total anomalous pulmonary venous drainage who had not been surgically treated. In 13 hearts the common pulmonary vein drained to the innominate vein, in 4 to the portal system, and in 3 to the region of the coronary sinus.

Results

The hemodynamic and echocardiographic data of the five patients with total anomalous pulmonary venous return are shown in Table I.

Echocardiographic contrast studies in two patients with an enlarged coronary sinus: These studies, performed during cardiac catheterization, showed a space posterior to an anomalous undulating echo complex at the A-V junction behind the aortic root. This space represented the enlarged coronary sinus. The space immediately anterior to this anomalous echo represented the left atrium, which was encroached on posteriorly by the enlarged coronary sinus (Fig. 1 and 2). The anomalous echo complex itself represented the echoes from the posterior left atrial and anterior coronary sinus walls.

Echocardiographic studies in total anomalous pulmonary venous drainage: Morphologically similar abnormal linear echoes were seen dorsal to the left atrium in the three patients with pulmonary venous drainage to the coronary sinus and in one patient with persistent left superior vena cava draining to the coronary sinus. These echoes were best visualized behind the aortic root at the A-V junction (Fig. 3). They were also well seen at a location posterior and superior to the tricuspid valve behind the right atrium in the patients with total anomalous pulmonary venous drainage to the superior vena cava or coronary sinus and they repre-

sented the right horn of the common pulmonary venous chamber (Fig. 4). The common pulmonary venous chamber was not detected in the one infant with anomalous pulmonary venous drainage to the portal system.

Phasic movements of echo complexes: These linear echo complexes behind the aortic root and the left atrium showed characteristic anterior motions during late ventricular diastole and mid systole (Fig. 3). The diastolic anterior motion was consistently observed between the P wave and the QRS wave of the electrocardiogram at the time of atrial systole. The systolic anterior motion followed the QRS complex of the electrocardiogram and had variable amplitude. These phasic movements reflect volume changes in the coronary sinus and the left atrium. During atrial systole the left atrium contracts with anterior movement of its posterior wall; there is presystolic emptying of the coronary sinus and diminution of its volume. However, during ventricular systole, when the right atrium is being filled from the systemic veins, coronary sinus flow is impeded, resulting in coronary sinus expansion and increased encroachment on the left atrium manifested in the echocardiogram by the systolic anterior motion of the anterior coronary sinus wall.

Echocardiographic measurements: Right ventricular enlargement and paradoxic interventricular septal motion were noted in all patients (Table I). The left atrium and left ventricle were small in four of the five patients with anomalous pulmonary venous drainage. The systolic time intervals of the right ventricle showed an abnormally increased ratio between preejection time and right ventricular ejection time in three of the four patients with elevated pulmonary arterial pressure.

Postoperative echocardiographic examinations: These studies failed to demonstrate the characteristic abnormal echo in the patients who had correction of total anomalous pulmonary venous drainage, but the echo was repeatedly observed in the patient with persistent left superior vena cava draining to the coronary sinus after repair of a secundum atrial septal defect.

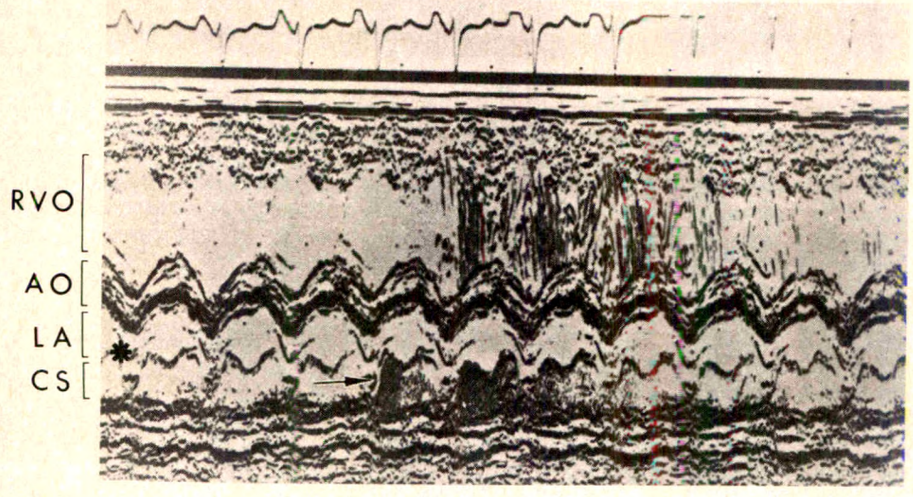


FIGURE 1. Case 6. Enlarged coronary sinus due to persistent left superior vena cava. Injection of 3 ml of 5 percent dextrose in water into the left superior vena cava shows initial opacification (**arrow**) of the coronary sinus (CS) posterior to the anomalous undulating echo (*) located behind the aortic root (AO) and left atrium (LA). The left atrium lies anterior to this anomalous echo and shows no echocardiographic contrast material. The right ventricular outflow tract (RVO) subsequently becomes heavily opacified because of forward flow from the right atrium. Note the distortion of the aortic root due to oblique angulation.

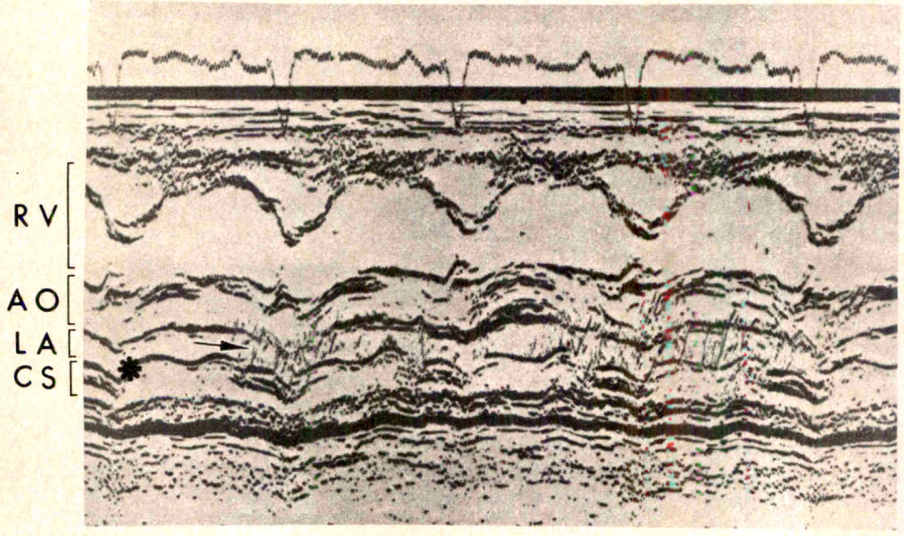


FIGURE 2. Case 3. Total anomalous pulmonary venous drainage with anomalous pulmonary venous return to the coronary sinus (CS). Injection of 3 ml of 5 percent dextrose in water into the left atrium (LA) shows opacification of this chamber (**arrow**); the space posterior to the anomalous echo (*) remains clear and indicates the position of the enlarged coronary sinus (CS). AO = aorta; RVO = right ventricular outflow tract.

Pathologic studies: These studies showed that in the three heart specimens in which the pulmonary veins returned to the coronary sinus, the enlarged coronary sinus was in close and consistent proximity to the posterior wall of the aorta. The aortic valve and the coronary sinus were in approximately the same horizontal plane, and the coronary sinus was related to the inferior part of the posterior wall of the left atrium as in the normal heart.

In the 13 heart specimens in which the pulmonary venous drainage entered the left superior vena cava by way of the innominate vein, the common pulmonary venous chamber lay posterior and superior to the level of the aortic valve. This chamber was directly posterior to the left atrium in four patients but was related only to the superior aspect of the left atrium in nine patients.

In the four heart specimens with infradiaphragmatic pulmonary venous return, the common pulmonary venous chamber formed the upper two limbs of a Y-

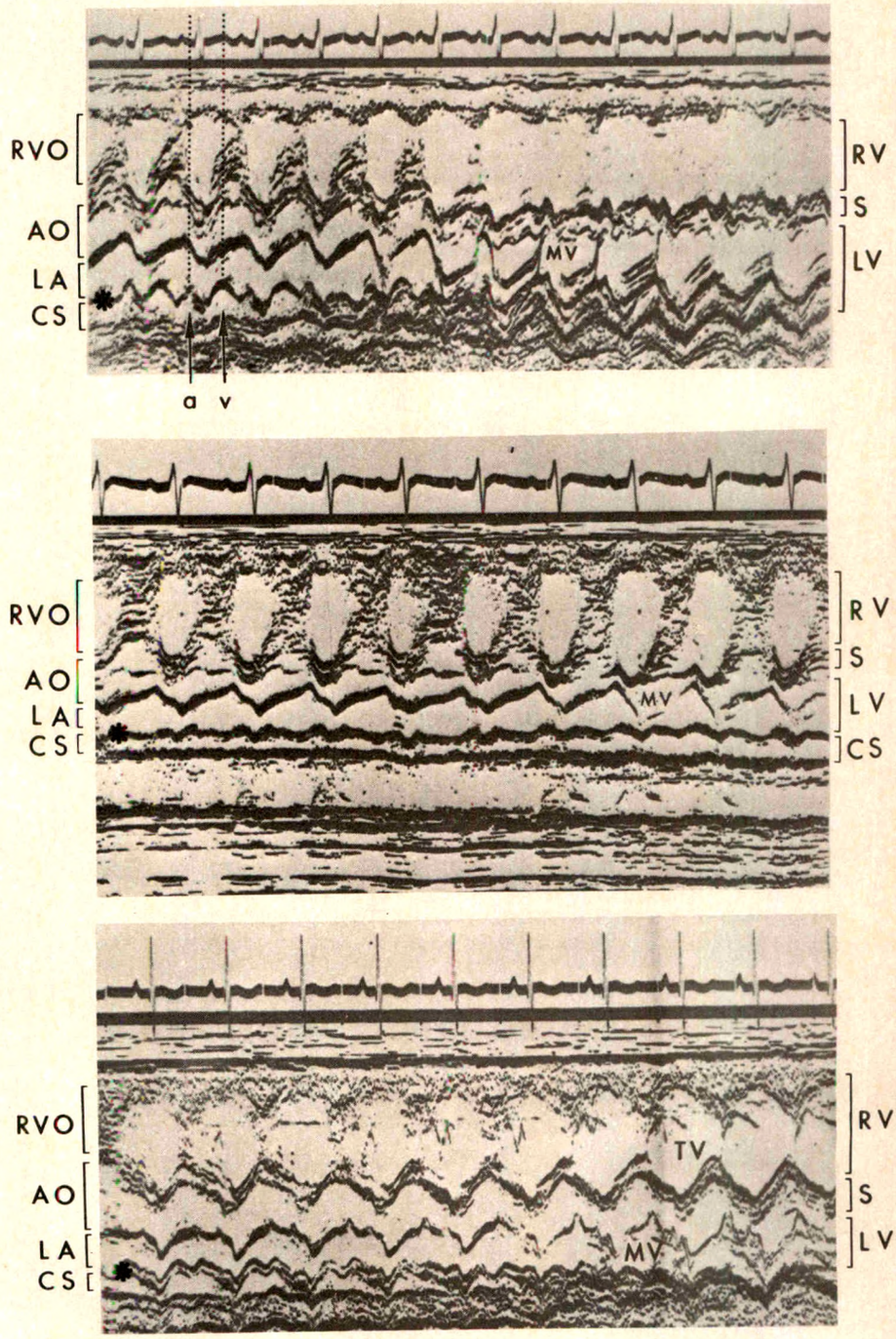
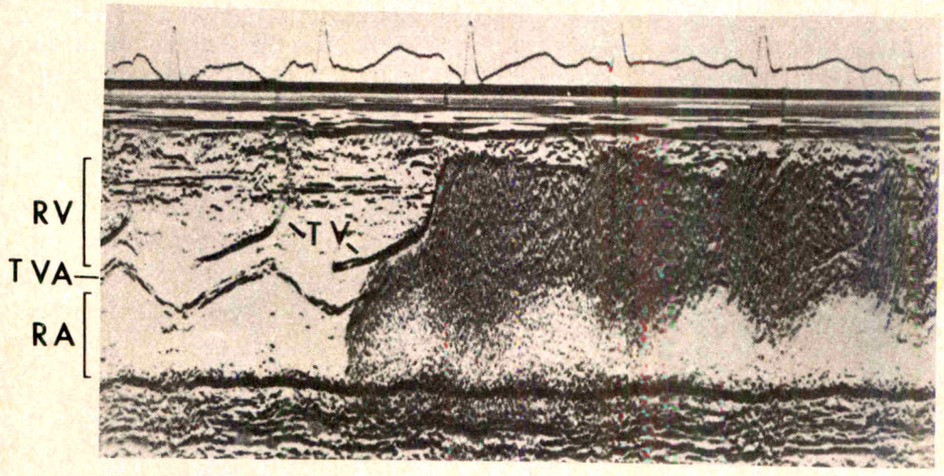
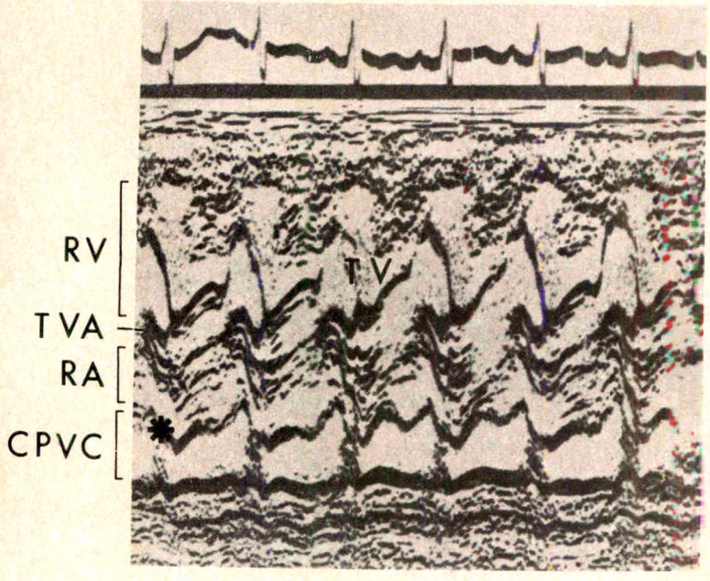


FIGURE 3. Scans from the aorta (AO) to the left ventricle (LV) in Cases 1 (**top**), 2 (**center**) and 3 (**bottom**) with total anomalous pulmonary venous drainage into the coronary sinus (CS) showing morphologically identical anomalous undulating echoes (*) at the A-V junction dorsal to the aortic root (AO) and left atrium (LA). Characteristic anterior motion of the anomalous echo is well seen during atrial (a) and ventricular (v) systole. This anomalous echo marks the anterior wall of the coronary sinus, and the thickened less mobile echo posterior to it demarcates the posterior wall of the coronary sinus. The left atrium is represented by the clear space between the coronary sinus and aortic root. MV = mitral valve; RV = right ventricle; RVO = right ventricular outflow tract; S = septum; TV = tricuspid valve.





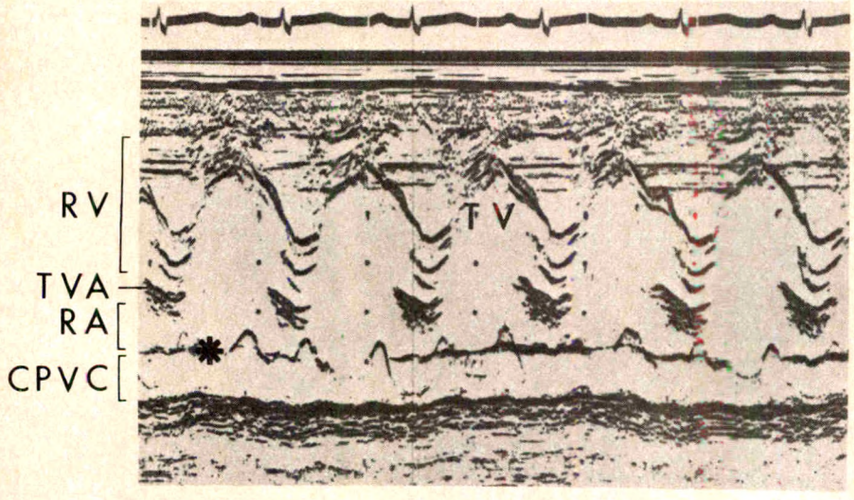


FIGURE 4. Top, tricuspid valve (TV) view in a child with coarctation of the aorta, obtained by placing the echocardiographic transducer at the low left parasternal region and angulating it so that the ultrasonic beam is directed rightward and superiorly. Five ml of 5 percent dextrose in water was injected into the right atrium (RA), which opacified first with subsequent opacification of the right ventricle (RV). Note the position of the tricuspid valve anulus (TVA). **Center and bottom,** similar tricupsid valve view in Cases 1 (**center**) and 5 (**bottom**), with total anomalous pulmonary venous drainage, showing an anomalous echo complex separating the right atrium (RA) anteriorly and the common pulmonary venous chamber (CPVC) posteriorly.

shaped structure. This chamber was caudal to the aortic valve and lay behind the posterior wall of the left atrium in two patients and was related only to the lowermost part of the left atrium in two (Fig. 5).

Discussion

Echocardiographic features of enlarged coronary sinus due to anomalous pulmonary venous drainage: Our study has shown that an abnormally enlarged coronary sinus, resulting from either anomalous pulmonary venous drainage or persistence of a left superior vena cava, can be detected posterior to the left atrium at the A-V groove using the aortic valve as a reference point. This structure is further characterized by a linear echo complex with distinctive systolic and diastolic phasic motion. The pathologic material indicates that when the coronary sinus is grossly enlarged, it encroaches on the dorsal aspect of the left atrium. The characteristic coronary sinus echo complex was detected at this site in all three patients with anomalous pulmonary venous return to the coronary sinus and, additionally, the right horn of the common pulmonary venous chamber was detected at a site posterior to the right atrium. However, no such chamber was seen behind the right atrium in the patient with persistent left superior vena cava draining to the coronary sinus, and this echocardiographic finding may serve as a distinguishing feature between these two causes of an enlarged coronary sinus. The normal-sized coronary sinus does not encroach on the posterior wall of the atria and is thus not detectable with the echocardiogram in normal hearts or hearts with other congenital malformations.

Spurious linear echoes of a different type, without a distinct phasic pattern, may be seen behind the aortic root in the left atrium of normal children and children with congenital heart disease.[9] In our experience these echoes are indistinct and interrupted and have no consistent oscillatory pattern during the cardiac cycle. Furthermore, they are not consistently visualized at any particular site, and with proper angulation can usually be made to disappear.

Total anomalous pulmonary venous drainage to sites other than the coronary sinus: This condition has not been consistently diagnosed echocardiographically by us or others. In this form of the anomaly, the pathologic material indicates considerable positional variation of the common pulmonary venous chamber with reference to the left atrium. In patients with supracardiac pulmonary venous return, the common pulmonary venous chamber was directly posterior to the left atrium in a few specimens but was related to its superior aspect in the majority. Thus, in most cases the common pulmonary venous chamber is near the superior aspect of the left atrium and lies far cephalad to the aortic valve: hence, a very oblique transducer angulation is required for its detection. In patients with subdiaphragmatic pulmonary venous drainage, the common pulmonary venous chamber was caudal to the aortic root and caudal to the inferior aspect of the left atrium in half of the specimens examined (Fig. 5). These variations in the relation of the common pulmonary venous chamber to the left atrium and the constraints placed on successful transducer alignment contribute to the difficulty in achieving a consistent diagnosis of this lesion with the single crystal M mode technique.

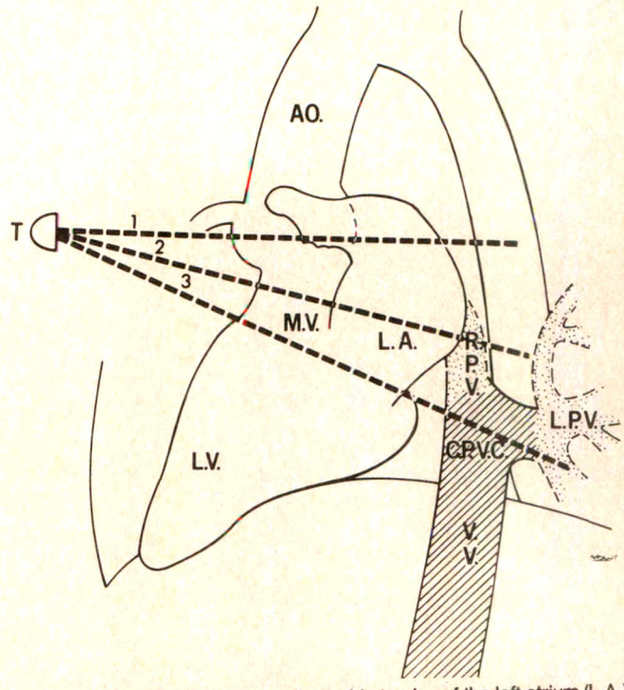


FIGURE 5. Lateral view cineangiographic tracing of the left atrium (L.A.) and the common pulmonary venous chamber (C.P.V.C.) from an infant with total anomalous pulmonary venous drainage to the portal system. The common pulmonary venous chamber lies inferior to the lower aspect of the left atrium and farther caudal to the aortic root (AO.) and would require a very oblique angulation of the ultrasonic beam (cross-bar scan position 3) to be detected. The right pulmonary veins (R.P.V.) lie to the right of the left atrium. L.P.V. = left pulmonary veins; L.V. = left ventricle; M.V. = mitral valve; T = transducer; V.V. = vertical vein.

References

1. **Tajik AJ, Gau GT, Schattenberg TT:** Echocardiogram in total anomalous pulmonary venous drainage. Mayo Clin Proc 47:247–250, 1972
2. **Goodman MJ, Tham, P, Kidd BSL:** Echocardiography in evaluation of the cyanotic newborn infant. Br Heart J 36:154–166, 1974
3. **Meyer RA, Kaplan S:** Noninvasive technique in pediatric cardiovascular disease. Prog Cardiovasc Dis 15:341–367, 1973
4. **Paquet M, Gutgesell H:** Echocardiographic features of total anomalous pulmonary venous connection. Circulation 51:599–605, 1975
5. **Tajik AJ, Gau GT, Ritter DG, et al:** Echocardiographic pattern of right ventricular diastolic volume overload in children. Circulation 46: 36–43, 1972
6. **Goldberg SJ, Allen HD, Sahn DJ:** Pediatric and Adolescent Echocardiography. Chicago, Year Book Medical Publishers, 1975, p 64
7. **Hirschfeld S, Meyer R, Schwartz DC, et al:** The echocardiographic assessment of pulmonary artery pressure and pulmonary vascular resistance. Circulation 52:642–650, 1975
8. In Ref 6, p 70
9. **William RG, Tucker CR:** Echocardiographic Diagnosis of Congenital Heart Disease, Boston, Little, Brown, 1977, p 64

Death From Ischemic Heart Disease in Young Finns Aged 15 to 24 Years

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The epidemiology and autopsy findings of death from ischemic heart disease were studied among 7,998 Finns who died at age 15 to 24 years between 1961 and 1971 (9,150,000 person-years). In 34 of this group, ischemic heart disease was indicated as the cause of death in the death certificate. Eight cases were excluded, six because of questionable evidence of ischemic disease and two because of the presence of another severe underlying disease. With 26 accepted deaths, the incidence of death from ischemic heart disease was 0.51/100,000 man-years and 0.04/100,000 woman-years, respectively. The World Health Organization criteria for acute ischemic heart disease were met in 21 cases (81 percent); in the remaining 5 cases, death had occurred suddenly with no other known cause. In 24 of 25 cases with a known time of onset of the fatal attack, death occurred within 24 hours of onset. The acute symptoms appeared during or immediately after physical exertion in 13 subjects (65 percent); in 5 of these the exercise was approximately maximal. Eight of 20 subjects with available data had a history of previous chest pain or arrhythmia. Autopsy was performed in 19 cases (73 percent). A stenosing process in the coronary arteries was found in 17 patients (89 percent). Among 15 to 19 year olds the stenosis was generally ostial and nonsclerotic; ostial stenosis was found in half of this group. After age 20, atherosclerosis was the major cause of coronary stenosis. The role and etiology of sclerotic and nonsclerotic coronary processes as a cause of acute ischemic heart disease in young persons are discussed.

The observation of a wide prevalence of atherosclerotic changes in the coronary arteries of young American soldiers in the Korean war[1] focused interest on latent coronary disease. The problem has been studied at autopsy in both middle-aged and young adults[2–5] and in children[6] and with exercise electrocardiography in middle-aged persons.[7] The results have varied considerably, especially in autopsy series, depending on the population studied, the age and sex of the subjects and the criteria used.[8] A representative study of atherosclerosis of the aorta and coronary arteries in five European towns (Malmö, Prague, Ryazan, Yalta and Tallin)[9] included 895 autopsy studies of patients aged 10 to 29 years: Greater than 50 percent stenosis of a coronary artery was occasionally found in men aged 20 to 24 years and in women aged 25 to 29 years.

Epidemiologic data on deaths from ischemic heart disease among middle-aged persons are available from vital statistics and also from community studies, such as those in Finland,[10] but corresponding data on young persons are scarce. Coronary heart disease was responsible for one third of sudden deaths in the 1940's among American soldiers less than 40 years old[11]; among Finnish conscripts aged about 20 years it accounted for 13 percent of sudden deaths from 1948 to 1972.[12]

The mortality rate from coronary heart disease among the middle-aged is highest in Finland according to World Health Organization

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TABLE I

Age and Sex Distribution in 26 Autopsy and Clinically Documented Deaths From Ischemic Heart Disease*

Age (yr)	Autopsy Cases: Sudden Deaths M	Autopsy Cases: Sudden Deaths F	Autopsy Cases: AIHD M	Autopsy Cases: AIHD F	Clinical Cases: Sudden Deaths M	Clinical Cases: Sudden Deaths F	Clinical Cases: AIHD M	Clinical Cases: AIHD F	Total
15	—	—	1	—	—	—	—	—	1
16	—	1	—	—	—	—	—	—	1
17	—	—	2	—	—	—	—	—	2
18	—	—	1	—	—	—	1	—	2
19	—	—	3	—	—	—	1	—	4
20	—	—	1	—	—	—	—	—	1
21	—	—	1	—	—	—	—	—	1
22	—	—	2	1	1	—	—	—	4
23	1	—	—	—	—	—	1	—	2
24	1	—	4	—	1	—	2	—	8
Total	2	1	15	1	2	—	5	—	26

* Deaths meeting World Health Organization criteria for acute ischemic heart disease (AIHD) and sudden deaths in subjects with no other known disease that could explain the death.

TABLE II

Duration of Acute Illness From Onset of Acute Symptoms to Death in Autopsy and Clinically Documented Cases

	Autopsy Cases	Clinical Cases	Total
Instant death	1	1	2
<15 min	7	—	7
≤59 min	3	1	4
≤1 hr, 59 min	1	—	1
≤11 hr	1	2	3
≤24 hr	—	1	1
<24 hr*	6	—	6
>24 hr	—	1	1
Unknown	—	1	1
Total	19	7	26

* Not otherwise specified.

statistics. This study describes the epidemiologic and autopsy findings in deaths due to ischemic heart disease among young Finns.

Material and Methods

The study population comprised a total of 830,000 Finns aged 15 to 24 years in 1961 to 1971, approximately 9,150,000 person-years. Deaths from ischemic heart disease[13] were studied. When ischemic heart disease was noted in the death certificate, the following documents were obtained and analyzed: (1) protocols of medicolegal autopsies, including data on circumstances of fatal illness, results of microscopic and histochemical examinations and findings of toxicologic analyses and of other examinations performed at autopsy; (2) outpatient and inpatient hospital records of deaths in hospitals and protocols of medical autopsies in these cases; and (3) data on medical history, circumstances of death and records of external examination of the corpse when death occurred outside the hospital and autopsy was not performed.

Ischemic heart disease was recorded in death certificates as the cause of death in 34 persons aged 15 to 24 years during the period of study. After a detailed analysis of the collected data, six cases were excluded because they did not meet the criteria for acute ischemic heart disease and the presence of other known diseases, as well as data on the fatal attack, suggested other mechanisms of death.

Acute ischemic heart disease was accepted as a cause of death in 28 young Finns, including 21 with autopsy confirmation. Two young men with autopsy verification of acute ischemic heart disease had a severe underlying disease: One, aged 21 years, had terminal juvenile diabetes with retinopathy and progressive uremia; the other, aged 23 years, had clinically diagnosed primary pulmonary hypertension with a typically progressive course. The exclusion of these two patients with "secondary ischemic heart disease" left a final series of 24 men and 2 women aged 15 to 24 years.

For the diagnosis of acute ischemic heart disease, the recommendations of World Health Organization[14] were followed. The criteria were: (1) chest pain as a cardinal symptom of fatal attack; (2) electrocardiographic changes typical of acute myocardial infarction; or (3) recent myocardial infarction or fresh coronary thrombosis verified at autopsy, or both (2) and (3). The criteria for sudden death were those proposed by Moritz and Morris.[15]

Results

Incidence of deaths and diagnostic criteria: The criteria for death from acute ischemic heart disease or sudden death (with no other known cause of death) in 1961 to 1971 were met by 24 deaths among Finnish men aged 15 to 24 years (incidence 0.51/100 000 person-years) and by 2 deaths among women (incidence 0.04/100 000 person-years). The regional distribution over the country was roughly even.

Ten victims (38 percent) were younger than 20 years (Table I), but the highest rate was found among those aged 24 years (31 percent of the series). Autopsy was performed in 19 of 26 cases (73 percent). The World Health Organization criteria for acute ischemic heart disease were met in 21 cases (81 percent), the electrocardiographic criteria in 2 clinical cases (age 19 and 24 years, respectively, Table I), the pathoanatomic criteria in 15 of 19 autopsy cases (see Table III) and chest pain as a symptom of the fatal attack in 3 clinical cases (age 18, 23 and 24 years, respectively, Table I) and in 1 autopsy case.

Fatal attack: Nearly all deaths occurred suddenly; in only one case did the fatal attack last longer than 24 hours (Table II). Most deaths (23 cases, 88 percent) occurred outside the hospital. Death occurred most frequently in the afternoon (11 cases) and least frequently at night (2 cases). Of the 20 subjects with data available on the onset of acute symptoms, 13 (65 percent) first experienced symptoms during or immediately after physical exertion; in 5 of the 13 the exertion was approximately maximal or near-maximal (intensive running or cycling, field maneuvers in the army, or similarly strenuous activity). Postprandial gastric distension was reported at autopsy in six subjects; in three of these the fatal attack was connected with strenuous physical exercise. Alcohol consumption shortly before death was verified in four men.

TABLE III

Disease History and Autopsy Findings in 19 Autopsy Cases

Case no.	Age (yr) Sex	Previous Symptoms	Heart Weight (g)	Recent MI	M	H	Coronary Thrombus	M	Coronary Artery Disease
1	15M	Chest pains	365	No	0	0	Yes	+	Stenosis of left ostium
2	16F	No	296	No	0	0	No	0	Nonsclerotic stenosis in RCA peripherally
3	17M	Unknown	400	Yes	0	0	No	0	Stenosis of left ostium
4	17M	Arrhythmias	370	Yes	0	+	No	0	Stenosis of left ostium + sclerotic plaques
5	18M	Arrhythmias	. . .	Yes	0	0	No	0	Stenosis of right ostium
6	19M	No	. . .	Yes	0	+	No	0	Hypoplasia and sclerotic plaque of LMCA
7	19M	Unknown	340	Yes	+	+	No	0	Sclerotic plaques
8	19M	No	354	No	0	0	Yes	+	Aneurysm in LAD
9	20M	Chest pain, dyspnea	420	No	−	0	No	−	Calcified stenosing nodules in RCA and LAD
10	21M	Chest pain, dyspnea	400	Yes	0	0	No	0	Sclerotic plaques
11	22M	No	400	No	0	0	Yes	+	Sclerotic plaques
12	22M	No	360	Yes	0	+	No	0	Sclerotic plaques
13	22F	No	230	Yes	0	+	No	0	No
14	23M	No	460	No	0	0	No	0	Sclerotic plaques
15	24M	Chest pains	. . .	Yes	0	0	No	0	No
16	24M	Arrhythmias	. . .	No	0	0	No	0	Sclerotic plaques
17	24M	Unknown	320	Yes	0	0	No	0	Sclerotic plaques
18	24M	No	349	Yes	+	0	No	0	Sclerotic plaques
19	24M	No	465	No	0	0	Yes	0	Sclerotic plaques

− = negative result; + = positive result; 0 = no examination performed; . . . = unknown; H = histochemical examination for myocardial infarction; LAD = left anterior descending coronary artery; LMCA = left main coronary artery; M = microscopic examination for myocardial infarction; MI = myocardial infarction ; RCA = right coronary artery.

Medical history: Data on previous disease or symptoms were available in 20 subjects. Eight men in this group (40 percent) had a history of chest pain or arrhythmia. In addition, in one subject in the clinical series (age 18, Table I), cardiac enlargement had been observed on mass miniature X-ray screening. Another subject in the clinical series (age 23, Table I) had a history of hereditary progressive muscular dystrophy. These two patients had chest pain as a cardinal symptom of their brief fatal attack. Hence, 10 of 20 subjects (50 percent) had a history of cardiac symptoms or a disease that can affect the heart muscle. On the other hand, in only one man had ischemic heart disease been suspected as a result of chest pain. This subject's death was sudden (age 24, Table I), and no autopsy was performed.

In most cases there was no family history of premature sudden death or of clinical myocardial infarction. A 19 year old man with coronary aneurysm verified at autopsy (Table III) had a brother who had died suddenly at age 18 years of unknown cause. No subject was known to have hyperlipidemia or to have had antilipidemic treatment, and no xanthomas were reported at autopsy.

Autopsy data: A recent myocardial infarction was found at autopsy in 11 subjects and a fresh coronary thrombosis in 4. Acute ischemic heart disease was thus verified in 15 of 19 autopsy cases (79 percent). In several cases the findings were confirmed with microscopic or histochemical studies (Table III).

A stenosing process in the coronary arteries was observed in 17 of 19 autopsy cases (89 percent) (Table III). Because these were routine autopsies, no exact estimates of the degree of stenosis were given. In men aged 20 to 24 years atherosclerotic plaques constituted the major stenosing process in the coronary arteries. In contrast, only one of the eight younger patients had atherosclerotic plaques as the only stenosing component of the coronary arteries. The aortic orifice of one coronary artery was the major stenotic site in half of the younger patients. In at least three of them the ostial stenosis was obviously nonsclerotic; there were no plaques in the coronary arteries or the aorta. The fourth man had, in addition to a marked stenosis of the aortic orifice of the left coronary artery, small plaques elsewhere in the coronary arteries. None of these four men had a history of infectious disease affecting the heart. In addition, a 19 year old man had a hypoplastic main trunk of the left coronary artery, which was additionally stenosed by a small plaque.

A 20 year old man had peculiar nodules, 10 to 15 mm in diameter and 15 to 25 mm in length, in the coronary arteries, two in the right coronary artery and one in the origin of the left anterior descending coronary artery. The nodules were heavily calcified and caused severe obstruction. This patient had had acute heart disease after an acute infection at age 5 years and had had symptoms since that time; he had chest pain during the fatal attack. At autopsy he was the only patient with a scar in the myocardium.

Of the two patients with no stenosing coronary artery disease at autopsy, one, a man aged 24 years, had a history of chest pain both before and during the fatal attack, the second, a woman aged 21 years, had no his-

tory of heart disease or symptoms and was 7 months pregnant when she died suddenly.

The mean heart weight at autopsy was 369 g (Table III). In no case did the thickness of the left ventricular wall exceed 15 mm. No subject had significant cardiac valve lesions, vascular disease or congenital defects except in the coronary arteries.

Discussion

When a young Finn dies from ischemic heart disease, detailed examinations are generally carried out. However, the validity of death certificates and of other health documents may be questioned in retrospective studies.[16] Of the 34 Finnish subjects aged 15 to 24 years in 1961 to 1971 whose death certificate indicated they died of acute ischemic heart disease, 6 were rejected for study because the documentation of the cause of death proved invalid and the data suggested some other mechanism of death than acute ischemic heart disease. After exclusion of two further cases with a severe underlying disease, the final series consisted of 26 deaths that either met the World Health Organization criteria for acute ischemic heart disease or were sudden deaths with no other known disease that could explain the death. Autopsy verification was obtained in 73 percent of cases.

Incidence: Deaths from ischemic heart disease were uncommon among Finns aged 15 to 24 years; the accepted cases gave an average rate of 0.28/100 000 person-years in 1961 and to 1971, that is, only about 1 percent of the disease mortality in this age group.[17] The male/female ratio was high (12:1) as expected.[18] The proportion of persons younger than 20 years (38 percent) was rather high compared with that of other studies.[18,19] However, the death rate was highest for those aged 24 (eight cases; 31 percent of the series). In eastern Finland the mortality rate from coronary heart disease among the middle-aged is the highest in the world, higher than in other parts of the country; however, among the young the deaths from ischemic heart disease were not concentrated in the east. In this age range death from ischemic heart disease is rare in all populations and is evidently caused by exceptional individual factors rather than general population characteristics.

Clinical features: Ischemic heart disease in young persons tends to occur suddenly: in 24 of our 25 subjects with available data, death occurred within 24 hours of the onset of the fatal attack. The suddenness of the fatal event seems to be an even more prominent feature in the young than in the middle-aged. For example, in the Ischemic Heart Disease Register of Helsinki, 73 percent of the deaths in men and 66 percent of those in women occurred within 24 hours.[10] On the other hand, we do not know how many myocardial infarctions were diagnosed in patients aged 15 to 24 years and how many patients recovered from their infarction in Finland in the study period. Because young people rarely have chronic myocardial damage, their chance of survival after hospitalization may be better than that of older patients with more frequent myocardial hypertrophy and old infarctions. Only one of our subjects had an old myocardial infarction verified at autopsy, and no subject had clear autopsy evidence of left ventricular hypertrophy.

Death, in addition to occurring suddenly, was also unexpected in at least half of the cases. Approximately 40 percent of the patients had previously had cardiac symptoms, chest pain or arrhythmia, but none had received drug therapy. Invariably, ischemic heart disease was diagnosed only during the fatal illness or after death. There appear to be few opportunities to predict sudden death from ischemic heart disease among the young, and such prediction may be possible only in exceptional cases. This conclusion is in agreement with the results of previous studies.[12,20]

Precipitating factors: Sudden death often occurred during physical exertion or immediately after it. Performance of maximal or near maximal physical exercise was known in 5 of the 20 cases in which data were available. Additional precipitating factors may have been exercise after eating and alcohol consumption shortly before the fatal event. Acute precipitating factors seem to be associated with sudden death more frequently in the young than has been reported among the middle-aged.[10]

Coronary ostial stenosis: A stenosing process in the coronary arteries was found at autopsy in a large proportion of cases (89 percent). Atherosclerotic plaques were considered the only cause of ischemic heart disease in only one of eight patients under age 20 years, however, coronary ostial stenosis was strikingly common (50 percent) in this age group. Nonsclerotic ostial stenosis is also found in a small proportion of older persons who die of ischemic heart disease.[21] In addition, one subject in our series had peripheral nonsclerotic stenosis and no history of symptoms. Because the stenotic sites were not examined with microscopy, the nature of the lesions cannot be defined. In principle, the lesions may be congenital or acquired. Three of our four subjects with ostial stenosis had a history of symptoms, arrhythmia or chest pain. No myocardial or cardiac valve signs of a previous rheumatic or infectious disorder could be demonstrated. Granulomatous arteritis (such as Takayasu's disease) can involve the coronary ostia.[22] However, no aortic lesions were recorded in our series. Nonspecific coronary arteritis, presumably viral in causation, may also result in luminal narrowing.[22] The postinfectious origin was obvious in a rare condition present in a man who had severely obstructing calcified nodules 10 to 15 mm in diameter in the left anterior descending and right coronary arteries. Arteritis, posttraumatic strictures and mural thickening with severe metabolic diseases have been reported as causing coronary stenosis, leading to ischemia.[22]

Congenital coronary anomaly: Two of our subjects had a probable congenital anomaly in the coronary arteries, that is, hypoplasia of the main left coronary trunk and a coronary aneurysm. Aneurysms may also be posttraumatic or postinfectious as a result of an infec-

tious embolus.[23] The congenital origin was supported in the latter patient by the lack of signs of endocarditis and by the history of his brother's sudden death.

Coronary atherosclerosis: In subjects aged 20 to 24 years, in contrast to the younger patients, the main cause of the coronary stenosis was atherosclerosis. A previous postmortem study of a Finnish series of violent deaths showed a significant raised lesion (surface area 50 mm^2 or more) in the coronary arteries in 1 of 15 men aged 15 to 19 (7 percent) and in 7 of 20 men aged 20 to 24 years (35 percent)[5]; in women the first raised lesions were found at age 30 years. The two women in our series had no coronary sclerosis. The findings in men suggest that under age 20, death from ischemic heart disease as a result of stenosing coronary atherosclerosis is extremely rare, but by age 25, the natural course of coronary atherosclerosis begins to take its first victims, particularly in a high risk population like Finland. No subject in our series had a known history of familial disturbance of lipid metabolism. A study of the risk factors among the relatives of our patients appears to be a natural follow-up to this study.

References

1. **Enos WF, Holmes RH, Beyer J:** Coronary disease among United States soldiers killed in action in Korea. JAMA 152:1090–1093, 1953
2. **Rigal RD, Lovell FW, Townsend FM:** Pathologic findings in the cardiovascular systems of military flying personnel. Am J Cardiol 6:19–25, 1960
3. **Mason JK:** Asymptomatic disease of coronary arteries in young men. Br Med J 2:1234–1237, 1963
4. **McNamara JJ, Molot MA, Stremple JF, et al:** Coronary artery disease in combat casualties in Vietnam. JAMA 216:1185–1187, 1971
5. **Rissanen V:** Aortic and coronary atherosclerosis in a Finnish autopsy series of violent deaths. Ann Acad Sci Fenn [Med] 155, 1972
6. **Strong JP, McGill HC Jr:** The pediatric aspects of atherosclerosis. J Atheroscler Res 9:251–265, 1969
7. **Cumming GR, Borysyk L, Dufresne C:** The maximal exercise ECG in asymptomatic men. Can Med Assoc J 106:649–653, 1972
8. **Enos WF, Beyer JC:** Coronary artery disease in younger men. JAMA 218:1434, 1971
9. **Kagan AR, Sternby NH, Uemura K, et al:** Atherosclerosis of the aorta and coronary arteries in five towns. Bull WHO 53:481–645, 1976
10. **Romo M:** Factors related to sudden death in acute ischaemic heart disease. Acta Med Scand [Suppl] 547, 1972
11. **Moritz AR, Zamcheck N:** Sudden and unexpected deaths of young soldiers. Diseases responsible for such deaths during World War II. Arch Pathol 42:459–494, 1946
12. **Koskenvuo K:** Sudden deaths among Finnish conscripts. Br Med J 2:1413–1415, 1976
13. International Classification of Diseases, 1965 revision, Vol 1. World Health Organization, Geneva, 1967, p 176–177
14. World Health Organization: Myocardial Infarction Community Registers. Public Health in Europe. 5. Copenhagen, Regional Office for Europe, WHO, 1976, p 157–161
15. **Moritz AR, Morris RC:** Handbook of Legal Medicine. Saint Louis, CV Mosby, 1970, p 18
16. **Penttilä A:** Mortality from Arteriosclerotic and Other Degenerative Heart Diseases in Finland in 1968. Helsinki, Health Services Research of the National Board of Health in Finland, 1975
17. Statistical Yearbook of Finland Year 1966, Helsinki, Central Statistical Office, 1967, p 64–65
18. **Moll A, Hamacher F:** Der Herzinfarct im jungeren Lebensalter. Enke, Stuttgart 1962, p 3
19. **Yater WM, Traum AH, Brown WG, et al:** Coronary artery disease in men eighteen to thirty-nine years of age. Am Heart J 36:334–372, 1948
20. **Balasubramanian V, Sahadevan MG, Hoon RS:** Sudden death in young Indians due to coronary artery disease. Indian Heart J 21: 339–341, 1969
21. **Rissanen V:** Occurrence of coronary ostial stenosis in a necropsy series of myocardial infarction, sudden death, and violent death. Br Heart J 37:182–191, 1975
22. **Cheitlin M, McAllistair HA, de Castro CM:** Myocardial infarction without atherosclerosis. JAMA 231:951–959, 1975
23. **Hudson REB:** Cardiovascular Pathology. I. London, Arnold, 1965, p 630–634

Remission of Clinical Angina Pectoris: the Framingham Study

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The anginal status of the Framingham cohort was ascertained in a uniform manner during 20 years of follow-up studies. There were 74 men and 84 women with newly acquired angina that was not complicated with other manifestations of coronary heart disease. Remission of new angina pectoris for at least 2 years occurred in 32 percent of the men and 44 percent of the women. In angina that had persisted for several years, the subsequent remission rates were lower (14 percent for men and 19 percent for women). The similarity of coronary risk attributes of subjects with transient or persistent angina supports the hypothesis that both conditions may be true manifestations of coronary artery disease. Persistence of symptoms seems to indicate a more severe form of the disease characterized by nonspecific S-T segment or T wave abnormalities. It is associated with a greater incidence of myocardial infarction and death than in subjects with transient angina. The generally high remission rates must be taken into account in considering drastic surgical or medical remedies for clinical angina pectoris. Also, other possible causes for the chest pain should be sought.

The clinical course of angina pectoris is becoming well documented, providing more precise estimates of the magnitude of the risk of myocardial infarction and death. However, the frequent occurrence of spontaneous remission of symptoms is often overlooked in the natural history of angina. This spontaneous remission rate is of particular importance in clinical trials evaluating various modes of therapy.

The cohort of the Framingham Heart Study has been under observation for the development of angina pectoris as well as other cardiovascular events for 20 years. The occurrence of anginal symptoms as well as their remission has been routinely documented. This report examines the frequency in the Framingham cohort of spontaneous remission of angina pectoris and its prognostic implications.

Methods

Angina pectoris is a clinical syndrome. It cannot be defined with the coronary angiogram or the exercise electrocardiogram because abnormalities indicated by these procedures are often unaccompanied by ischemic chest pain. Like any laboratory test, a history of angina has a technical error that impinges on its validity and reliability. On evaluating the prognosis of presumed angina pectoris according to the severity of coronary artery disease judged from angiography or the exercise electrocardiogram, patients with negative findings will have a more favorable prognosis. This raises the question whether these fortunate persons have "true" angina. Because there is no test specific for ischemic chest pain, there is no way to resolve this issue. This study of the prognosis of intermittent angina suffers from the same problem. Nevertheless it has relevance in evaluating what is basically a clinical syndrome.

Study protocol: The Framingham Study documented the occurrence in the cohort of all cases of angina pectoris by means of a standardized medical history

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78-80	5	0	2	DECK NO.	VERIFIED BY		DATE
1-4					RECORD NUMBER		
					CHEST IN INTERIM:		
5	No 0	Yes 1	Maybe 2	Unk. 9	CHEST DISCOMFORT		
					When Does Chest Discomfort Occur?	— + with exertion or excitement — + When quiet or resting	
					— + Repeated Short Episodes	DATE OF ONSET	USUAL DURATION
						LOCATION	LONGEST DURATION
						RADIATES TO	FREQUENCY
						TYPE	
						Relieved by: NG—+0; Rest—+0;	Spont.—+
					— + Prolonged Episodes (describe)		COMMENTS
6	No 0	Yes 1	Maybe 2	Unk 9	ANGINA PECTORIS	1ST EXAMINER'S OPINION	
7	0	1	2	9	CORONARY INSUFFICIENCY		
8	0	1	2	9	MYOCARDIAL INFARCTION		
9	No 2nd Exam. 3	0	1	2	9	ANGINA PECTORIS	2ND EXAMINER'S OPINION
10	3	0	1	2	9	CORONARY INSUFFICIENCY	
11	3	0	1	2	9	MYOCARDIAL INFARCTION	
						(Page 3)	

FIGURE 1. Form used to obtain medical history.

included in the routine biennial examinations (Fig. 1). The medical examination also included a detailed investigation for the occurrence of other cardiovascular disease and certain other historical information, as well as measurements of many physiologic characteristics. Out-of-clinic surveillance for disease was maintained by a review of hospital and physician records, medical examiners' reports and death certificates.[1] Follow-up has been reasonably complete, 85 percent responding to each examination. Follow-up for death was more complete, with only 2 percent lost to follow-up.[2]

Although not ideal, the Framingham Study offers a more comprehensive than usual assessment of the natural history of angina in general and of spontaneous remissions in particular. The natural history is available not only for persons who sought medical care but also for those who did not seek it or continue under such care. Only slightly more than half of patients with angina were taking medication for relief of symptoms. During the period reported on, no patient had cardiac surgery.

Diagnosis of angina: Angina is a subjective phenomenon, and its diagnosis is uniquely dependent on a history of chest discomfort and based on an evaluation of symptoms little different from the original description by Heberden[3] in 1772. Although physical findings during the attack, the exercise electrocardiogram and the associated coronary risk profile may all help to clarify the problem, the diagnosis of angina ultimately depends on a careful evaluation of symptoms. A variety of anginal syndromes have been described, including unstable angina, impending infarction, Prinzmetal's angina, intermediate syndrome and crescendo angina.[4–8] However, stable recurring angina with attacks of brief duration, provoked by exertion and promptly relieved by rest, is the most common and securely founded entity.

In the Framingham Study, angina was diagnosed when symptoms of substernal distress of short duration (less than 15 minutes), distinctly related to exertion and relieved by rest or nitroglycerin, were elicited. All suspected cases were confirmed by a second examining physician, and the diagnosis was rejected if the findings were not consistent or another explanation was found. No electrocardiographic findings, either at rest or with exercise, were required for a diagnosis.[9]

A cardiovascular history designed to elicit symptoms of angina was administered to each subject every 2 years. The data on appearance and disappearance of angina must be considered in the context of these 2 year intervals. We are not describing daily or monthly variation in symptoms. *Persistent uncomplicated* angina pectoris was defined as angina that was not complicated by other clinical manifestations of coronary heart disease and that persisted at least one examination after the examination of onset (that is, for two consecutive biennial examinations). *Transient uncomplicated* angina pectoris was defined as uncomplicated angina that was followed by a negative history of interim angina on the next examination. Additionally, it was required that no other clinical manifestation

TABLE I

Frequency of Persistent and Transient Uncomplicated Angina Pectoris

	Men		Women	
	no.	%	no.	%
Persistent*	50	68	47	56
Transient	24	32	37	44
Total	74	100	84	100

* The difference between men and women in percent of those with persistent angina is not statistically different from 0.

TABLE II

Prognosis After Persistent Versus Transient Uncomplicated Angina Pectoris

	no. With Uncomplicated Angina Pectoris	Percent Dead in 4 Years
Persistent*		
Men	50	20
Women	47	11
Transient*		
Men	24	0
Women	37	3

* Chi-square test, null hypothesis: Percent dead with persistent angina pectoris equals percent dead with transient angina pectoris; probability (P) <0.05.

of coronary heart disease occur in the interim examination after the onset of angina.

Results

During the first eight biennial examinations of the Framingham Heart Study (1948 to 1966), 74 men and 84 women experienced uncomplicated angina pectoris of either a transient or a persistent nature (Table I). By the definition given, the angina in 32 percent of men and in 44 percent of women was transient in character. Thus, remissions of at least 2 years' duration were fairly common.

Persistent versus transient angina: The prognosis of persistent angina was substantially worse than that of the short-term transient angina. In men, 20 percent of those with persistent angina were dead within 4 years (Table II). In contrast, no deaths occurred in the same interval in men whose angina had disappeared. The more severe prognosis of persistent angina was also seen in women. Because there is little difference in the age distribution of the patients with persistent or transient angina, age differences cannot account for this difference in mortality. The incidence of myocardial infarction was also greater in patients with persistent angina (Table III). No infarctions were observed in 4 years among patients of either sex with transient angina.

TABLE III

Myocardial Infarction (MI) After Persistent Versus Transient Uncomplicated Angina Pectoris

	no. With Uncomplicated Angina Pectoris	Percent With MI in 4 Years
Persistent*		
Men	50	12
Women	47	6
Transient		
Men	24	0
Women	37	0

Chi-square test, null hypothesis: Percent of subjects with persistent angina pectoris having a myocardial infarction equals percent of subjects with transient angina having a myocardial infarction (probability [P] <0.05).

Risk factors in persistent versus transient angina: The better prognosis in subjects whose angina disappeared for 2 or more years could be a consequence of a faulty diagnosis because no objective criteria were employed. However, the profile of risk attributes at the time of diagnosis suggests that this is not the case (Table IV). The levels of systolic blood pressure, serum cholesterol, relative weight and left ventricular hypertrophy are not statistically different in the groups with transient or persistent angina. The mean ages are almost identical in the two groups. Only the prevalence of nonspecific T wave or S-T segment abnormalities is greater in the group with persistent angina. The similarity of predisposing factors in the two groups suggests

TABLE IV

Attributes in Transient and Persistent Uncomplicated Angina Pectoris: Framingham Heart Study, Men and Women

	Uncomplicated Angina Pectoris					
	Men			Women		
	Transient	Persistent	Significance	Transient	Persistent	Significance
Mean systolic blood pressure (mm Hg)	142	139	NS	165	163	NS
Mean serum cholesterol (mg/dl)	248	246	NS	275	271	NS
Mean relative weight (%)	124	123	NS	130	132	NS
Left ventricular hypertrophy (%)	8	14	NS	14	26	NS
Nonspecific T or S-T abnormality (%)	8	32	P <0.05	19	19	NS
Mean age (yr)	57.5	58.4	NS	60.6	60.1	NS
Cases (no.)	24	50		37	47	

NS = not significant; P = probability.

TABLE V

Patterns of Angina in Those With Persistent Uncomplicated Angina Pectoris (History at Biennial Examinations After Onset)

Persistent at			% Distribution	
2 Yr	4 Yr	6 Yr	Men	Women
+	−	−	14	19
+	+	−	6	14
+	−	+	11	8
+	+	+	69	58

+ = present; − = absent.

that the cases of transient angina are not misdiagnosed. Therefore it appears that disappearance of symptoms in itself indicates an improved prognosis in cases of true angina.

Late remission of persistent angina: Even persistent angina shows frequent subsequent remissions. Table V records data from subjects who were alive and whose history was available for two examinations after their initially persistent symptoms. Of those who had a positive history of angina on two consecutive examinations, 69 percent of men and 58 percent of women continued to have angina for a total of four consecutive examinations. The others had varying patterns of remissions and recurrences, including 14 percent of the men and 19 percent of the women who reported no angina for two examinations after previously persistent symptoms.

Discussion

When a patient is allowed to progress from being a high risk candidate for coronary disease to having symptomatic angina pectoris, he is likely to have major occlusive disease of one or more coronary arteries.[10] When the neglected candidate for coronary disease has reached this stage, he really constitutes a medical failure rather than a first indication for treatment. Nevertheless, there are many patients with established angina who seek relief from their symptoms and protection against the high risk of disability, myocardial infarction, congestive failure and premature death.

Natural history of angina pectoris: In considering therapy to relieve the suffering and disability of the patient with angina, it is helpful to know the true natural history of established stable angina. Although the angina can be incapacitating, most patients adjust to the disease reasonably well and are able to live within their exercise tolerance. Few are forced to give up their usual line of work. Because physicians mainly encounter patients with the more serious complaints, angina has a reputation of being a severely disabling disease.

Although the presence of angina does increase the risk of subsequent morbidity and mortality, this is not uniformly so. Symptoms in a substantial percent of patients actually disappear, and this remission seems to indicate a better prognosis than persistent symptoms.

Other sources[11,12] have noted a remission of symptoms for long periods of time or permanently, even after angina had been present for many months or years. Friedberg[11] attributed this remission to the development of collateral circulation or to fibrosis of the ischemic myocardium as a result of eventual complete coronary occlusion. Angina has been noted to subside or disappear completely with the development of congestive heart failure or permanent atrial fibrillation. Remission in these cases has been attributed to a reduction in physical activity imposed by these cardiac complications.[11]

Although specific data are sparse, it is the impression of most clinicians that remissions are uncommon. Blumgart[13] noted that "... in a small proportion of patients marked temporary improvement may occur, evidently owing to the development of adequate collateral channels to regions of myocardial ischemia, or the correction of associated conditions such as thyrotoxicosis or anemia. An occasional patient may indeed be permanently relieved of the distress."[13] The Framingham data suggest that remission is much more common than this passage indicates.

Mechanisms for remission of angina: The mechanism responsible for the disappearance of angina is not well established. Theoretically it should follow development of collateral circulation to compensate for the compromised circulation to the ischemic segment of myocardium. More often it probably follows a decrease in demand put on the heart as the patient learns to live within his exercise tolerance.

Relief of angina pectoris and improved cardiac performance under a work load must be related to either an improved supply of oxygen and blood to the heart or to a reduced oxygen demand. The major determinants of myocardial oxygen demand include the intramyocardial tension (intraventricular pressure, ventricular volume and myocardial mass), the heart rate and the contractile state.[14] The tension-time index has been used as an index of myocardial oxygen demand.[15] An examination of the tension-time index at rest in the Framingham Study (product of heart rate and systolic blood pressure) in those who had a remission versus those with established angina pectoris did not reveal any significant differences. Evidently myocardial oxygen consumption in the *resting state* is not related to the loss of angina.

The claim that angina is often eliminated by an interim infarction that destroys the ischemic myocardium responsible for the pain is not supported by our data. Interim infarctions were less, not more, common in those whose angina disappeared. The better prognosis of patients with transient angina is also inconsistent with this hypothesis.

Diagnostic and prognostic implications: It is possible that those whose angina disappeared promptly or whose angina was intermittent did not in fact have angina. Coronary angiographic studies frequently fail to show significant coronary artery disease in patients suspected of having angina. There is no way to exclude this possibility definitely, although the risk factor

profile of the subjects with transient angina was similar to that of patients with persistent angina.

It is not clear from these data what the proper conclusion should be. Does true angina often go into remission and, when it does, does the remission indicate a good prognosis? Or is it that when a remission occurs it is wise to consider and seek out another cause for the chest pain? Angiography was not performed in these subjects, but this procedure would not really settle the matter either. Severe coronary artery disease may be evident in an angiogram in patients with no chest pain. There is no escaping the fact that angina pectoris is a clinical syndrome and a physiologic state. It is not an anatomic condition or an electrocardiographic abnormality at rest or with exercise. Frequently, persons with blatantly positive ischemic electrocardiographic exercise responses have no chest pain either during the exertion or between tests. Angina as diagnosed in this study by experienced investigators, using a structured examination procedure, whether associated with myocardial infarction or not, carries a distinctly worse than average risk of myocardial infarction and death. This lends some substance to the possibility that all of these patients have "true" angina. In any event, no other explanation for the chest pain was uncovered even after prolonged observation.

Therapeutic implications: Unless aggressive medical and surgical remedies are confined to persistent and truly incapacitating clinical angina, there is every indication that the treatment may be more dangerous than the disease. Transient or remittent clinical angina appears to be another contraindication to coronary bypass surgery and hazardous medical treatment. Angiographic and physiologic investigation of why a substantial amount of angina disappears may shed some light on the reason for the excellent prognosis and may suggest better remedies for the condition than those currently available. More detailed *routine* studies to exclude other possible causes of chest pain in subjects with remittent angina to determine how often this angina is on some other basis would also seem indicated.

References

1. **Shurtleff D:** Some characteristics related to the incidence of cardiovascular disease and death. The Framingham Study, Section 30 (Pub no. NIH 74-599). Washington, DC, Dept of Health, Education, and Welfare, 1974
2. **Kannel WB:** Some lessons in cardiovascular epidemiology from Framingham. Am J Cardiol 37:269–282, 1976
3. **Heberden W:** Some account of a disorder of the breast. M Tr Roy Coll Phys 2:59–67, 1772
4. **Prinzmetal M, Ekmekci A, Kennamer R, et al:** Variant form of angina pectoris, previously undelineated syndrome. JAMA 174: 1794–1800, 1960
5. **MacAlpin RN, Kattus AA Jr:** Angina pectoris at rest with preservation of exercise capacity—"angina inversa." Circulation 36: Suppl II:II-176–II-177, 1967
6. **Graybiel A:** The intermediate coronary syndrome. US Armed Forces Med J 6:1–7, 1955
7. **Freedberg AS, Blumgart HL, Zoll PM, et al:** Coronary failure: the clinical syndrome of cardiac pain intermediate between angina pectoris and acute myocardial infarction. JAMA 138:107–114, 1948
8. **Gazes PC, Mobley EM Jr, Faris HM Jr, et al:** Pre-infarctional (unstable) angina—a prospective study—ten-year follow-up. Prognostic significance of electrocardiographic changes. Circulation 48:331–337, 1973
9. **Kannel WB, Feinleib M:** Natural history of angina pectoris in the Framingham study. Am J Cardiol 29:154–163, 1972
10. **Humphries JO, Kuller L, Ross R, et al:** Natural history of ischemic heart disease in relation to arteriographic findings. Circulation 49:489–497, 1974
11. **Friedberg CK:** Diseases of the Heart. Philadelphia, WB Saunders, 1966, p 746
12. **Duncan B, Fulton M, Morrison SL, et al:** Prognosis of new and worsening angina pectoris. Br Med J 1:981–985, 1976
13. **Blumgart HL:** Diseases of the coronary arteries. In, A Textbook of Medicine, 10th edition (Cecil RL, Loeb RF, ed). Philadelphia, WB Saunders, 1959, p 1274–1282
14. **Varnauskas E, Bergman H, Houk P, et al:** Hemodynamic effects of physical training in coronary patients. Lancet 2:8–12, 1966
15. **Sarnoff SJ, Braunwald G, Welch GH Jr, et al:** Hemodynamic determinants of oxygen consumption of the heart with special reference to tension-time index. Am J Physiol 192:148–156,1958

Disease of the Left Main Coronary Artery

Surgical Treatment and Long-Term Follow Up in 267 Patients

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Of 4,196 patients undergoing coronary angiography, 297 (7 percent) had left main coronary arterial narrowing. In 188 (4.5 percent) the narrowing was greater than or equal to 70 percent and in 109 (3 percent) it was between 50 and 69 percent. Three patients (1 percent) died at cardiac catheterization. Saphenous vein bypass graft surgery was performed in 267 patients with an operative mortality of 7 percent: in 179 patients the left main coronary narrowing was greater than or equal to 70 percent (operative mortality 9 percent), and in 88 between 50 and 69 percent (mortality rate 2 percent). There was an average of 2.6 grafts per patient. The course of these patients was followed up for 4 3/4 years. At 1 year there was a 92.2 percent survival rate. The rate of survival at 2, 3 and 4 3/4 years, was 91, 89 and 86 percent, respectively. After saphenous vein bypass graft surgery, 75 percent of patients are angina-free and 22.4 percent are in improved condition. Grafts were studied in 51 patients and 85 percent of 128 grafts were found to be patent. It appears that there is improvement in survival and a reduction of symptoms after saphenous vein bypass graft surgery in patients with left main coronary arterial narrowing.

Significant narrowing of the left main coronary artery has received considerable attention. It is the coronary lesion most often associated with impaired quality of life because it is so frequently attended by angina pectoris,[1–3] and it has a formidable yearly mortality rate when treated medically.[1,2] Coronary bypass surgery can commonly be accomplished at an acceptable risk in patients with left main coronary arterial narrowing,[2–6] and previous reports have shown that these patients have an improved quality of life and increased longevity with such treatment.[1–3,7,8] We therefore analyzed the various features of our patients with this disease and attempted to assess the results of surgery. Accordingly, this report describes in detail the course of 267 patients with left main coronary artery disease who underwent coronary bypass surgery at this medical center from November 9, 1970 through December 30, 1975.

Methods

Patients: Coronary arteriograms obtained between August 1, 1970 and December 12, 1975 were reviewed. There were 4,196 patients studied by coronary arteriography during this period. Of these, 297 (7 percent) had left main coronary arterial narrowing of at least 50 percent. These 297 patients constituted the total study group. The angiograms were reviewed independently by at least one cardiologist, a cardiac radiologist and a cardiac surgeon. Left main coronary narrowing compromising the luminal diameter by 50 percent or more was considered "significant." Coronary arteriography was performed with either the Sones (180 patients) or Judkins (108 patients) method.

The right anterior oblique projection of the left ventriculogram (and sometimes also the left anterior oblique projection) was qualitatively and quantitatively evaluated for both localized and generalized disorders of myocardial contraction, and the ejection fraction was determined in the right anterior oblique plane.

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Follow-up of all patients was completed through December 1975 by sending questionnaires regarding the patient's current status to the referring physician. In some instances, when the returned information was incomplete, one of us contacted the patient by telephone. The survival curve was constructed with the actuarial method.

Clinical features: Thirty of the 297 patients with significant left main coronary arterial narrowing who underwent coronary arteriography did not undergo coronary bypass surgery. Of these, three (1 percent of the total) died either during or within 24 hours after coronary arteriography. All three had more than 70 percent narrowing of the left main coronary artery, and in all three the narrowing was located proximally in the left main coronary trunk. One of the three patients had unstable angina with multiple episodes of pain at rest both before and during the angiographic procedure.

Of the 27 remaining patients who did not undergo bypass surgery to the left coronary artery, 9 had more than 70 percent and 18 had 50 to 69 percent luminal narrowing in this vessel. Three of the nine with more than 70 percent narrowing had sufficient distal involvement of the coronary tree to preclude adequate bypass surgery. Two died late after catheterization from coronary causes, one died of cancer and three are still surviving and continue to have angina. Of the 18 with 50 to 69 percent narrowing, 3 underwent right coronary bypass surgery because the left coronary vessels could not be technically bypassed. The remaining 15 were not operated on because they had poor distal vessels or refused surgery. There were three late postcatheterization deaths in these 18 patients. A group of 15 patients thus survived; 11 of these continue to have angina and 4 are angina-free.

Two hundred sixty-seven (267) patients underwent coronary arterial bypass surgery. There were 227 men and 40 women. The age ranged from 26 to 75 years (average 58); 13 patients were older than 69 years. One hundred thirty-six patients (51 percent) had had a previous transmural myocardial infarction as evidenced by the presence of diagnostic Q waves in the electrocardiogram. Of these, 112 had had one myocardial infarction, and 24 had had two myocardial infarctions. Twenty-one of the 267 patients (8 percent) had a history of congestive heart failure. Angina was the dominant symptom in the immediate preoperative period in all but 10 patients who subsequently underwent surgery. The preoperative angina class (New York Heart Association criteria[9]) was class II in 77 patients (29 percent), class III in 94 (35 percent) and class IV in 86 (32 percent). Of these 86 patients, 19 (7 percent) were considered to have unstable angina (Table I).

Table II summarizes the angiographic assessment of decreased left ventricular function. Left ventricular function was considered severely abnormal if the ejection fraction was between 0.10 and 0.29, moderately abnormal if it was between 0.30 and 0.49 and normal or mildly abnormal if it was above 0.50. The ejection fraction was severely reduced in 23 patients (8 percent) (less than 0.20 in 6), moderately reduced in 80 patients (29 percent) and normal or mildly reduced in 164 patients (61 percent).

On the basis of the Cleveland Scar Code,[10] 133 patients had no left ventricular scar, 79 had one scar, 11 had two scars, 30 had generalized akinesia and 14 had a discrete left ventricular aneurysm.

Surgical procedures performed: A single bypass graft was performed in 12 patients (4.5 percent). This graft was made to the anterior descending, circumflex or diagonal branch of the left coronary artery (Table III). Double bypass grafts were performed in 103 patients (39 percent). Of these grafts, 23 were performed in patients with two vessel disease involving the left main coronary artery plus one of the other left branches, and 80 (30 percent) in patients with three vessel disease (left main coronary, left coronary branches and right coronary artery). Triple bypass grafts were performed in 127 patients (48 percent) and quadruple bypass grafts in 24 (9 percent). Ninety-three patients (35 percent) were considered to have incomplete vascularization; that is, they had a greater number of stenosed coronary arteries than could be successfully grafted.

Saphenous vein grafts were used in more than 80 percent

TABLE I

Status of Angina* in 267 Patients With Left Main Coronary Arterial Narrowing Undergoing Coronary Bypass Surgery

Class I	Class II	Class III	Class IV	Unstable†
10 (3.7%)	77 (29%)	94 (35%)	86 (32%)	19 (7%)

* New York Heart Association criteria.[9]
† Included in class IV.

TABLE II

Angiographic Evaluation of Left Ventricular Function in 267 Patients

Ejection Fraction			
0.10–0.19	0.20–0.29	0.30–0.49	>0.50
6 (2.2%)	17 (6.4%)	80 (30%)	164 (61%)

Cleveland Scar Code[10]				
Normal	1 Local Scar	2 Local Scars	Aneurysm	Diffuse Scar (generalized akinesia)
133 (51%)	79 (29.6%)	11 (4%)	14 (5.2%)	30 (11%)

TABLE III

Analysis of Bypass Grafts in 267 Patients*

	Number of Bypass Grafts			
	1	2	3	4
Site of 2 Vessel Disease				
LMCA only	3	1	1	...
LMCA + LAD	3	8	1	...
LMCA + LCx		5	2	...
LMCA + LAD + LCx	2	9	2	...
Total	8	23 (9%)	6 (2%)	...
Site of 3 Vessel Disease				
LMCA + RCA	1	3	2	...
LMCA + RCA + LAD	1	18	12	1
LMCA + RCA + LCx		4	14	2
LMCA + RCA + LAD + LCx	2	56	93	21
Total	4	80 (30%)	121 (45%)	24 (9%)
Total	12 (4.5%)	103 (39%)	127 (48%)	24 (9%)

* Total 697 bypass grafts; 2.6 grafts per patient. LAD = Left anterior descending coronary artery; LCx = Left circumflex coronary artery; LMCA = left main coronary artery; RCA = right coronary artery.

TABLE IV

Associated Procedures in 267 Patients With Coronary Bypass Surgery*

None	238 (89%)
Mitral valve repair	6 (2.2%)
Aneurysm resection	6 (2.2%)
Right coronary arterial endarterectomy	16 (6%)
Left coronary arterial endarterectomy	1 (0.3%)

* Average number of grafts per patient: 2.6.

of patients; 50 patients had internal mammary artery-left anterior descending coronary anastomosis. There was an average of 2.6 grafts per patient (697 grafts in 267 patients).

Twenty of the patients operated on had mitral regurgitation of a variable degree; mitral valve repair was performed in six of these (2 percent) (Table IV). Left ventricular aneurysm resection was performed in 6 other patients (2 percent) and associated right coronary endarterectomy in 16 patients (6 percent).

Results

Significant Postoperative Complications

Perioperative acute myocardial infarction (with pathologic Q waves) occurred in 19 patients (7 percent). None of these patients died and none demonstrated significant hemodynamic impairment in the postoperative period.

Operative mortality: Eighteen patients died in the hospital or during the first 60 days postoperatively (total operative mortality rate 7 percent). Seven of these patients had circulatory failure during cardiopulmonary bypass and could not be weaned from the pump. Notably, some of these patients had intractable circulatory collapse before our perioperative use of intraaortic balloon pump assistance. Three postoperative deaths occurred in patients with a severely abnormal ejection fraction and all of these died with cardiogenic shock. In one woman who had had a double vein graft (right coronary and left anterior descending arteries) occlusion of the right brachial artery developed, and she had a cardiac arrest while undergoing exploration of that artery in the postoperative period. She was found to have an acute myocardial infarction and one clotted vein graft at autopsy. Another patient had a cardiac arrest in the operating room before operation, and an extensive myocardial infarction developed; this patient died 3 days postoperatively with heart failure. Three patients sustained hypoxic encephalopathy and cardiogenic shock after operation. One patient had an extensive cerebrovascular accident in the perioperative period and experienced hemiparesis and coma. One patient died postoperatively of an adult respiratory distress syndrome accompanied by renal failure. One patient died 18 days postoperatively of a disseminated intravascular coagulation syndrome with massive pulmonary embolism and a resultant adult respiratory distress syndrome. One patient died 2 months postoperatively of renal failure, mediastinitis and generalized sepsis. Fourteen patients had transient episodes of hemiparesis that subsequently cleared.

TABLE V

Postoperative Status of 267 Patients Undergoing Coronary Bypass Surgery

Asymptomatic	174	(65%)
Angina		
Class II	52	(20%)
Class III	3	(1%)
Class IV	3	(1%)
Myocardial infarction		
Perioperative	19	(7.1%)
Late	8	(3%)
Death		
Early coronary	18	(6.75%)
Late coronary	10	(3.74%)
Noncoronary	4	(1.5%)
Reoperation at other institution and postoperative death	1	

Results of Long-Term Follow Up

Surgical group: Of the 267 patients, there were 249 survivors of operation (18 surgical deaths) who were followed up from 2 to 62 months postoperatively (average 28 months). Fifty-three patients were followed up for up to 12 months; 61 have been followed up for 24 months, 53 for 36 months, 50 for 48 months and an additional 32 for up to 60 months.

One hundred seventy-four of the 249 surviving patients (70 percent) are now free of angina and 52 (21 percent) have class II angina (Table V). Eight patients (3 percent) had a nonfatal myocardial infarction in the late postoperative period. Six of these patients died 15 or more months after the operative procedure. One patient had a recurrence of angina and was operated on 43 months after the initial operation at another hospital and died on the 2nd postoperative day. Four patients died of noncoronary causes. Table VI shows an analysis of the total group of 297 patients according to the number of diseased vessels.

Medically treated group: Results in the 30 patients who did not undergo left coronary bypass surgery were not statistically analyzed because the group was small and had a shorter follow-up period (mean 17.98 months, range 0 to 46 months) than the surgical group. In this group, 12 patients had left main coronary narrowing greater than or equal to 70 percent. Three of these died at cardiac catheterization. Of the remaining nine patients, two (22 percent) died from cardiovascular causes within the follow-up period and one died of a noncardiac-related cause. Eighteen patients in this group had left main coronary arterial narrowing of 50 to 69 percent.

TABLE VI

Survival of Patients According to Number of Diseased Coronary Arteries

Vessels Involved (no.)	Patients (no.)		
	Alive	Dead	Total
0	3	2	5
1	26	1	27
2	60	9	69
3	171	25	196
Total	260	37	297

Three of these (17 percent) died of coronary causes related to coronary artery disease during the follow-up period.

Surgical mortality related to ventricular function: When viewed from the standpoint of ventricular ejection fraction, the surgical mortality was as follows: In the 23 patients with a severely reduced ejection fraction there were four surgical deaths (17 percent mortality rate); in the 80 patients with a moderately reduced ejection fraction there were nine surgical deaths (11 percent mortality rate); and in the 164 patients with a normal or only mildly reduced ejection fraction, there were five surgical deaths (3 percent mortality rate).

Survival related to internal mammary artery graft (Table VII): The patients who had a left internal mammary artery graft to the left anterior descending coronary artery, alone or in combination with a saphenous vein bypass graft to other vessels, were analyzed separately in an effort to determine whether their survival time was significantly different from that of patients who had only saphenous vein bypass grafts. There were 50 such patients. Four of these (8 percent) died within the follow-up period. Of the 217 patients who received only saphenous vein bypass grafts, 20 (13 percent) died in the follow-up period. A chi square test applied to these data indicates that the observed differences were not statistically significant.

TABLE VII

Results in 267 Surgically Treated Patients According to Type of Procedure

	IMA	SVG Only	Totals
Survived	46	188	234
Any death	4 (8%)	29 (13%)	33 (12%)
Total patients	50	217	267

IMA = left internal mammary artery anastomosis alone or in combination with saphenous vein grafting; SVG = saphenous vein graft.

Discussion

Major narrowing of the left main coronary trunk as defined in this study represents an important element in the spectrum of coronary artery disease. The presence of significant narrowing of the left main trunk almost certainly assures diminution in the quality of life because most patients with this lesion have considerable angina pectoris. Moreover, the presence of left main coronary arterial narrowing almost always implies significant disease in other branches of the coronary tree.[4,5,8,11–14] Because of the large amount of left ventricular myocardium subserved by the divisions of the left main artery, and because of the presence of multiple additional lesions, it might be speculated that myocardial infarction caused by occlusion of the left main trunk would be potentially catastrophic more often than other forms of myocardial infarction. Although there is no direct evidence to support this speculation, it is indirectly substantiated by the high yearly mortality rate in patients with this lesion treated medically. Zeft et al.[4] reported a high incidence rate of severe left ventricular decompensation and left ventricular aneurysm formation in nonsurgically treated patients with occlusion of the left main trunk. Subsequent attempts at aneurysmectomy in their severely ill patients led to an 83 percent perioperative mortality rate. The yearly rate of subsequent infarction in nonsurgically treated patients with left main disease was 33 percent, a rate exceeding that even in patients with triple vessel disease.

Risk from cardiac catheterization: Our data reveal that angiographic study of the coronary arterial tree in patients with significant disease of the left main coronary artery is feasible within acceptable limits of risk. The mortality rate attributed to cardiac catheterization in our group was 1 percent (3 of 297 patients); all 3 patients had 70 percent or greater narrowing located quite proximally in the left main coronary trunk. These limited data may indicate that proximal lesions have the greatest risk, perhaps because the arteriographic catheter virtually occludes the entire blood supply to the branches of the left coronary artery when narrowing is very proximal. This speculation is supported by the work of Bassan et al.,[15] who found that intubation of the left coronary artery ostium with normal angiographic catheters causes a decisive reduction in coronary sinus blood flow (a reflection of left coronary arterial blood flow) and coronary catheter tip pressure only in those patients with significant main left coronary lesions. Furthermore, catheter-induced spasm or secondary local edema from catheter manipulation could potentially further compromise left coronary arterial blood flow. In fact, the 1 percent mortality risk from catheterization is 10 times greater than the risk in our laboratories for other patients with coronary disease. However, of the three deaths, one occurred in a patient who was virtually in status anginosus; it is therefore difficult to be certain that the procedure itself was the cause of his death. A second patient died of myocardial infarction 24 hours after his procedure and, again, the possibility that his death was not related to angiography must be considered. Our patients were studied with both major coronary arteriographic techniques and neither procedure carried more risk than the other. This finding agrees with the experience of others[4,8] who noted no increase in morbidity or mortality with the Judkins technique.

Effect on angina: The total or marked relief of angina experienced postoperatively by most of our patients is consistent with the previous observations on all types of coronary bypass surgery and, specifically, with those of reports considering bypass surgery in patients with left main coronary disease.

Late survival: Although no large study of patients treated medically for left main coronary artery disease has appeared thus far, previous authors have indicated an annual mortality rate of 15 to 35 percent in these patients.[2,3,5,10,13] Our surgically treated patients had an 8 percent mortality rate in the 1st year postoperatively and rates of 1, 2.5 and 0.5 percent mortality at 2, 3, and 4 3/4 years, respectively. Figure 1 is a set of actuarial curves based on our data and projected to 5 years. Thus, it appears that survival is substantially improved in

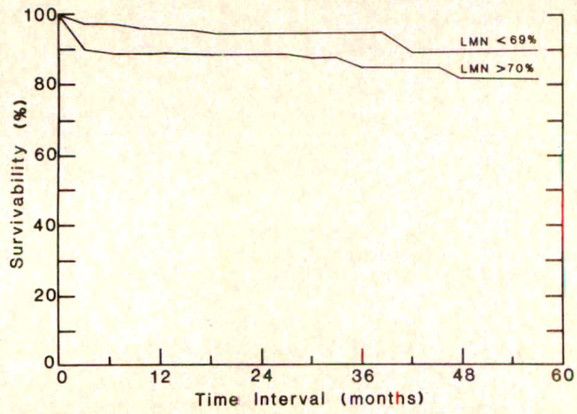

FIGURE 1. Survival of surgically treated patients having more than 70 percent as compared with less than 69 percent left main (LMN) coronary arterial narrowing.

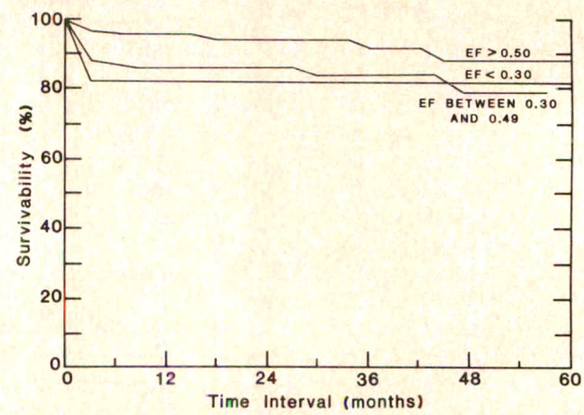

FIGURE 2. Analysis of survival of surgically treated patients with left main coronary arterial narrowing and reduced left ventricular function (ejection fraction [EF]).

surgically treated patients with left main coronary artery disease when they are compared with patients whose lesion is treated medically. This finding has been reported by previous authors.[2,4] The majority of our surgical deaths occurred within the 1st year and, of course, many of these are related to immediate postoperative and perioperative complications. This finding suggests an even greater benefit from the effects of revascularization once the immediate hazards of surgery are past.

The data in Figure 2 indicate an increased risk, particularly at the time of operation, for patients with a compromised left ventricle. Nevertheless, even in these very debilitated patients, prospects for longer survival are good when surgery is the mode of treatment.

Survival related to degree of left main coronary stenosis: Our data suggest that, although surgically treated patients generally have an increased survival, there is a measurable difference in the survival time of surgically treated patients with less than 69 percent stenosis and those with more than 70 percent stenosis of the left main coronary artery. Figure 1 shows that 97 percent of the former group were alive 36 months after operation compared with only 86 percent of the latter. At 48 months these figures were 88 and 82 percent, respectively. This difference in mortality was almost entirely due to a higher operative death rate in the patients with more severe left main stenosis. The gap in survival between the two groups thus established at the time of operation remained essentially unchanged through the subsequent 4 to 5 year follow-up period.

Implications: On the basis of the data presented and their correlation with results of previous studies of patients with left main coronary artery disease, we believe that these patients should be studied and operated on without undue delay. It appears that the angiographic evaluation of such patients is within acceptable risk limits and that coronary bypass grafting is the treatment of choice in this group. The data also support previous findings indicating not only an improvement in the quality of life, but also a significant increase in the longevity of such patients.

References

1. **Pichard AD, Sheldon WC, Shinji K, et al:** Severe arteriosclerotic obstruction of the left main coronary artery: follow-up results in 176 patients (abstr). Circulation 48:Suppl IV:IV-53, 1973
2. **Cohen MV, Gorlin R:** Main left coronary artery disease: clinical experience from 1964–1974. Circulation 52:275–285, 1975
3. **McConahay DR, Killen D, McAllister D, et al:** Coronary artery bypass surgery for left main coronary artery disease. Am J Cardiol 37:885–889, 1976
4. **Zeft HJ, Manley JC, Huston JH, et al:** Left main coronary stenosis: results of coronary bypass surgery. Circulation 49:68–76, 1974
5. **Lavine P, Kimbiris D, Segal BL, et al:** Left main coronary artery disease: clinical, arteriographic and hemodynamic appraisal. Am J Cardiol 30:791–796, 1972
6. **Sung RJ, Mallon SM, Richter SE, et al:** Left main coronary obstruction: follow-up of thirty patients with and without surgery. Circulation 52:Suppl I:I-112–I-118, 1975
7. **Talano JV, Scanlon PJ, Jhan M, et al:** Influence of surgery on survival in 145 patients with left main coronary disease. Circulation 50:Suppl III:III-110, 1974
8. **DeMotts J, Bonchek LI, Rosch J, et al:** Left main coronary artery disease: risks of angiography, importance of coexisting disease of other coronary arteries and effects of revascularization. Am J Cardiol 36:136–141, 1975
9. Criteria Committee of the New York Heart Association: Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels, seventh edition. Boston, Little, Brown, 1973, p 286
10. **Bruschke AG, Proudfit WL, Sones FM, Jr:** Progress study of 590 consecutive non-surgical cases of coronary disease followed 5–9 years. II. Ventriculographic and other correlations. Circulation 47:1154–1163, 1973
11. **Lim JS, Proudfit WL, Sones FM, Jr.:** Left main coronary arterial obstruction: long-term follow-up of 141 nonsurgical cases. Am J Cardiol 36:131–135, 1975
12. **Cutler SJ, Ederer, F:** Maximum utilization of the life table method in analyzing survival. J Chronic Dis 8:699–712, 1958
13. **Berkson J, Gage RP:** Calculation of survival rates for cancer. Proc Mayo Clin 25:270–286, 1950
14. **Cohen MV, Cohn, PF, Herman MV, et al:** Diagnosis and prognosis of main left coronary artery obstruction. Circulation 45:Suppl I:I-57–I-65, 1972
15. **Bassan MM, Ganz W, Marcus HS:** Effect of left coronary artery catheterization on coronary blood flow. Circulation 48:Suppl IV: IV-142, 1973

Pharmacokinetics and Bioavailability of Digoxin Capsules, Solution and Tablets After Single and Multiple Doses

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The bioavailability of single doses of digoxin capsules (0.4 mg), digoxin solution (0.4 mg) and reference tablets (0.5 mg) was compared with that of single intravenous doses (0.4 mg) of digoxin using measurement of 24 hour urinary excretion and area under the plasma concentration curve. The absolute systemic availability of all three oral preparations was significantly less than 100 percent. The bioavailability of capsules and solution was nearly identical (79 percent and 76 percent, respectively, as assessed with values for area under the concentration curve and 65 percent and 62 percent as assessed with urinary excretion values); both forms had greater systemic availability than the tablet, which had bioavailability values of 50 percent using area under the curve and 41 percent using urinary excretion. Capsules and solution also were similar in peak plasma digoxin levels achieved (3.7 and 3.1 ng/ml), time of peak concentration (0.8 and 0.6 hour after dosage) and apparent first order absorption half-life (11.3 and 10.2 minutes); both capsules and solution differed significantly from tablets (peak level 1.6 ng/ml, time of peak concentration 1.2 hours and absorption half-life 27.1 minutes). Single dose findings were substantiated when steady state plasma levels and 24 hour urinary excretion values were measured from days 11 through 16 of the period of once daily ingestion. Mean plasma levels (0.70 ng/ml) and urinary excretion values (45.1 percent of dose) for capsules were nearly identical to those for solution (0.69 ng/ml and 42.5 percent of the dose), and values for both capsules and solution were significantly greater than those for tablets. Within- and between-subject variation in bioavailability was similar for the three oral preparations. Thus the single dose bioavailability study was predictive of the steady state findings. The bioavailability of digoxin capsules is equivalent to that of a solution and significantly greater than that of a reference tablet formulation.

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Achievement of stable and predictable plasma digoxin concentrations during long-term digoxin therapy remains difficult because all currently available oral digoxin preparations are incompletely and variably absorbed from the gastrointestinal tract.[1] An optimal fixed dose oral digoxin preparation would have a predictable high level of bioavailability with minimal variation in the extent of absorption within and between subjects. Gelatin capsules containing digoxin in solution reportedly have improved bioavailability and may be a potential replacement for digoxin tablets.[2–8] However, the extent of improved bioavailability of capsules and the issue of whether steady state plasma digoxin levels are less variable than with existing standard preparations have not been settled by previous studies. We investigated the extent and variability of digoxin absorption from the capsule preparation after single and multiple doses in comparison with those of standard reference tablets and solution.

Methods

Subjects: Twelve healthy male volunteers (Table I) served as experimental subjects after giving informed consent. None had any demonstrable medical disease.

Procedure: Each subject received the following four digoxin preparations in random sequence:

Solution: 0.4 mg reference standard digoxin dissolved in 2 ml of U.S.P. ethanol and 198 ml of water. The container was rinsed with 40 ml of water, which was also ingested.

Tablets: Two 0.25 mg tablets of reference standard digoxin (Lanoxin®, Burroughs Wellcome Co., lot no. 022-I, with an in vitro dissolution rate of 75 percent in 1 hour).

TABLE I
Pharmacokinetic Variables After Intravenous Administration of Digoxin

Case no.	Age (yr)	Weight (kg)	$t_{1/2\alpha}$ (hr)	$t_{1/2\pi}$ (hr)	$t_{1/2\beta}$ (hr)	V_1 (liters/kg)	V_d (liters/kg)	Clearance (ml/kg per min)
1	33	80.0	*	*	*	*	*	*
2	29	80.9	0.05	0.42	63.01	0.128	10.95	2.01
3	29	81.8	0.19	1.02	37.88	0.252	8.43	2.59
4	34	84.5	0.44		10.03	0.306	4.06	4.68
5	25	79.5	0.32		10.19	0.501	6.77	7.76
6	26	82.7	0.15	0.85	46.21	0.309	14.50	3.63
7	29	65.9	0.39		11.07	0.577	7.83	8.17
8	27	72.7	0.41		27.70	0.621	8.79	3.66
9	24	68.2	0.43		16.34	0.534	6.87	4.85
10	23	68.2	0.24		9.70	0.315	3.15	3.74
11	27	77.3	0.06	0.66	27.73	0.179	8.75	3.65
12	29	81.8	0.06	0.62	46.21	0.168	12.43	3.11
Mean	27.9	77.0	0.24	0.71	27.82	0.35	8.41	4.35
SE	±1.0	±1.9	±0.04	±0.10	±5.54	±0.053	±1.01	±0.59
Composite		77.0	0.14	0.61	19.3	0.28	6.72	4.47

* Indicates that least-squares analysis could not be performed because of outlying data points.
SE = standard error; $t_{1/2\alpha}$ = distribution half-life; $t_{1/2\pi}$ = intermediate half-life; $t_{1/2\beta}$ = elimination half-life; Vd = total apparent volume of distribution; V_1 = volume of central compartment.

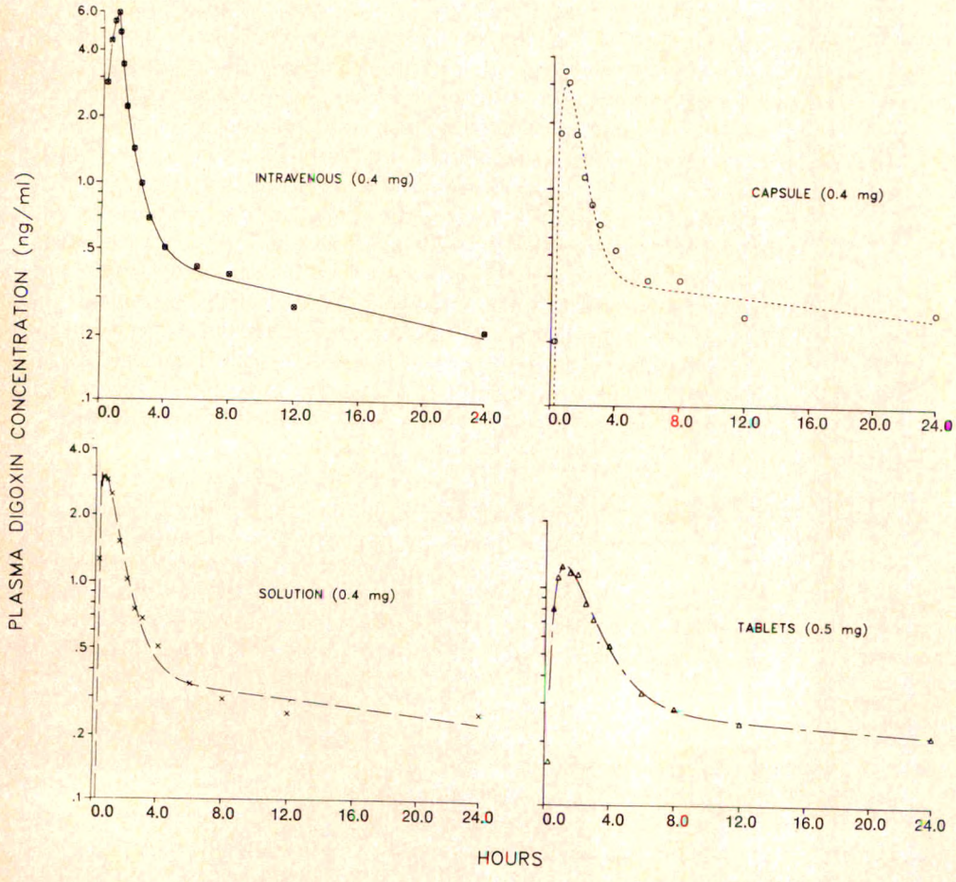


FIGURE 1. Plasma digoxin concentrations after administration of a single dose of intravenous digoxin and of the three oral digoxin preparations. Each point is the mean for all 12 subjects at the time shown (standard errors, omitted for clarity, will be provided by the author on request). Also shown are the pharmacokinetic functions determined from least-squares regression analysis (see text).

TABLE II
Pharmacokinetics of Digoxin Absorption From the Three Oral Preparations

Case no.	Capsule (0.4 mg)				Solution (0.4 mg)				Tablet (0.5 mg)			
	Peak Level (ng/ml)	Peak Time (hr after dose)	Lag Time (min)	$t_{1/2a}$ (min)	Peak Level (ng/ml)	Peak Time (hr after dose)	Lag Time (min)	$t_{1/2a}$ (min)	Peak Level (ng/ml)	Peak Time (hr after dose)	Lag Time (min)	$t_{1/2a}$ (min)
1	3.5	1.0	*	*	3.3	0.75	11.8	11.0	2.1	0.75	14.4	4.2
2	3.5	1.0	*	*	2.5	0.5	11.5	7.2	0.6	1.5	15.0	74.3
3	3.2	0.75	*	*	2.5	0.5	10.7	11.2	0.9	2.0	*	*
4	4.1	0.75	28.2	3.1	2.8	0.5	*	*	1.2	1.0	13.8	31.3
5	2.3	0.75	14.4	24.9	1.3	1.0	14.2	34.3	1.0	1.5	17.4	36.8
6	3.1	0.75	15.0	19.0	3.0	0.75	10.8	9.8	1.8	0.75	14.4	17.6
7	2.8	0.5	15.0	3.5	2.9	0.5	13.7	1.0	1.7	1.0	11.4	7.0
8	5.7	0.75	*	*	4.1	0.75	12.6	6.5	2.9	1.5	12.0	35.6
9	4.0	1.0	15.0	19.9	2.7	0.5	8.6	8.1	1.3	2.0	*	*
10	2.9	0.75	29.6	0.9	3.2	0.75	14.4	13.1	2.0	1.0	13.8	31.5
11	4.2	0.75	12.6	7.6	5.0	0.5	9.8	6.1	1.6	0.5	15.0	0.7
12	4.8	0.75	15.0	12.4	3.9	0.5	12.5	4.2	1.5	1.0	11.4	32.0
Mean	3.7	0.8	18.1	11.3	3.1	0.6	11.9	10.2	1.6	1.2	13.9	27.1
±SE	±0.3	±0.04	±2.4	±3.1	±0.3	±0.04	±0.6	±2.6	±0.2	±0.1	±0.6	±6.8
Composite	3.4	0.75	15.0	19.8	2.9	0.5	11.4	7.4	1.2	1.0	12.4	22.0

* Indicates that least-squares analysis could not be performed because of outlying data points.

Capsules: Two 0.2 mg capsules of digoxin prepared in a liquid-filled soft gelatin capsule (Arnar-Stone Laboratories, lot. no. 746P).

Intravenous preparation: 0.4 mg of digoxin injection (Lanoxin®, lot no. 994-S) diluted with 48.4 ml of sterile 5 percent dextrose in water and infused into an antecubital vein by a constant rate infusion pump over 1 hour.

Tablet and capsule preparations were ingested with 240 ml of water. Subjects fasted overnight before each oral dosage trial and abstained from further food or liquid for 4 hours after drug administration. Venous blood samples were drawn through an indwelling catheter, or by venipuncture, before dosage and 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3, 4, 6, 8, 12 and 24 hours after digoxin ingestion or the start of infusion. Additional samples were drawn at 65 and 75 minutes after the start of intravenous infusion. A 24 hour urine collection was begun at the time of digoxin administration.

After the initial 24 hours of study, each oral preparation was taken daily at 9 AM for 14 additional days. "Steady state" blood samples were collected just before the daily dose on days 11 through 16. Urine was collected in 24 hour periods after doses 11, 12, 13, 14 and 15. After the final dose of each oral preparation, 24 hours of blood sampling was performed as in the case of the initial dose. Subjects remained ambulatory during testing, and at least 14 days elapsed between each trial to permit complete excretion of digoxin from the preceding period.

Analysis of plasma and urine: Plasma and urine samples were stored at −20° C until the time of assay. Digoxin concentrations in plasma and urine were determined with radioimmunoassay as previously described.[9,10]

Analysis of data: Plasma digoxin concentrations after intravenous infusion were analyzed with the computer using iterative nonlinear least-squares regression techniques,[11,12] as described in detail elsewhere.[13] Data points for individual subjects, as well as for composite points calculated as the across-subject mean plasma concentrations at corresponding points in time, were fitted to bi- or triexponential functions consistent with two- or three-compartment pharmacokinetic models. The functions of best fit were then used to calculate the following pharmacokinetic variables[13–16]: distribution half-life ($t_{1/2\alpha}$), intermediate pi half-life ($t_{1/2\pi}$) when appropriate, elimination half-life ($t_{1/2\beta}$), volume of the central compartment (V_1), total apparent volume of distribution using the area method (V_d) and total clearance.

After oral administration of digoxin, individual and composite data points were similarly analyzed and fitted to the sum of the smallest number of exponential terms necessary to describe the data adequately. Fitted functions were used to calculate the lag time (t_0) elapsing before the start of first order absorption, and the apparent first order absorption half-life ($t_{1/2a}$). In all cases iterative analysis proceeded until the convergence criteria were met or 50 iterative steps were completed.

Plasma digoxin concentrations for the 24 hours after the first and last dose of each preparation were used to calculate the area under the 24 hour plasma concentration curve using the trapezoidal method. Single dose bioavailability was assessed by comparing the area under the plasma concentration curve and the 24 hour urinary excretion values after each preparation, using repeated-measures analyses of variance and the Newman-Keuls test of paired comparisons.[17] Relative bioavailability of the three oral preparations during long-term therapy was similarly assessed from steady state plasma concentrations and urinary excretion values. Appropriate adjustments were made for differences in oral doses of tablets, capsules and solution.

Between- and within-subject variations in the various measures of bioavailability were expressed as coefficients of variation. The between-subject coefficient of variation for a given mode of treatment was determined as the standard deviation for that treatment divided by the treatment mean, expressed in percent. When multiple measurements were made for the same subjects within a given treatment, an overall within-subject coefficient of variation for that treatment was calculated by weighted pooling of each individual subject's coefficient of variation.[18]

Results

Single dose pharmacokinetics: Figure 1 shows single dose composite data points for all four modes of digoxin administration, together with functions of best fit.

Disappearance of digoxin from plasma after intravenous infusion was best fitted by two exponential phases in six subjects and by three exponential phases in five subjects (Table I). In the remaining subject (Case 1), a satisfactory fit could not be achieved because of outlying data points. The mean apparent elimination half-life was 27.8 hours, the total volume of distribution 8.4 liters/kg and the total clearance 4.35 ml/min per kg. These values are consistent with data in other reports of intravenous digoxin pharmacokinetics in normal subjects.[19]

Peak serum digoxin concentrations (in ng/ml) averaged 3.7 after capsule administration, 3.1 after solution, and 1.6 after tablets (Table II). Analyses of variance indicated that the overall difference among preparations was significant ($F = 46.5$, d.f. = 2,22, $P < 0.001$). The difference between capsule and solution also was significant ($P < 0.05$). The peak level was attained an average of 0.8 hour after dosing with capsules, 0.6 hour with the solution, and 1.2 hours with tablets. Again the overall difference was significant ($F = 11.9$, d.f. = 2,22, P

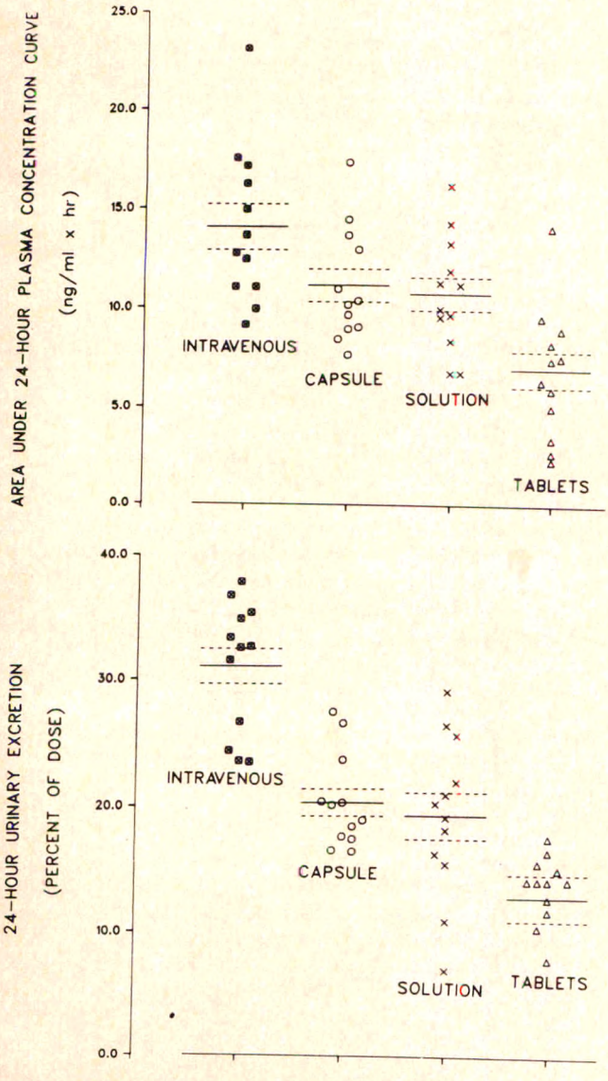


FIGURE 2. Area under the 24 hour plasma concentration curve (**above**) and 24 hour urinary excretion rate of digoxin (**below**) after a single dose of intravenous digoxin and of the three oral digoxin preparations. Individual values and means (± standard error) for all subjects are shown. Values for area under the 24 hour plasma concentration curve after administration of tablets (**above**) were corrected for the difference in dose.

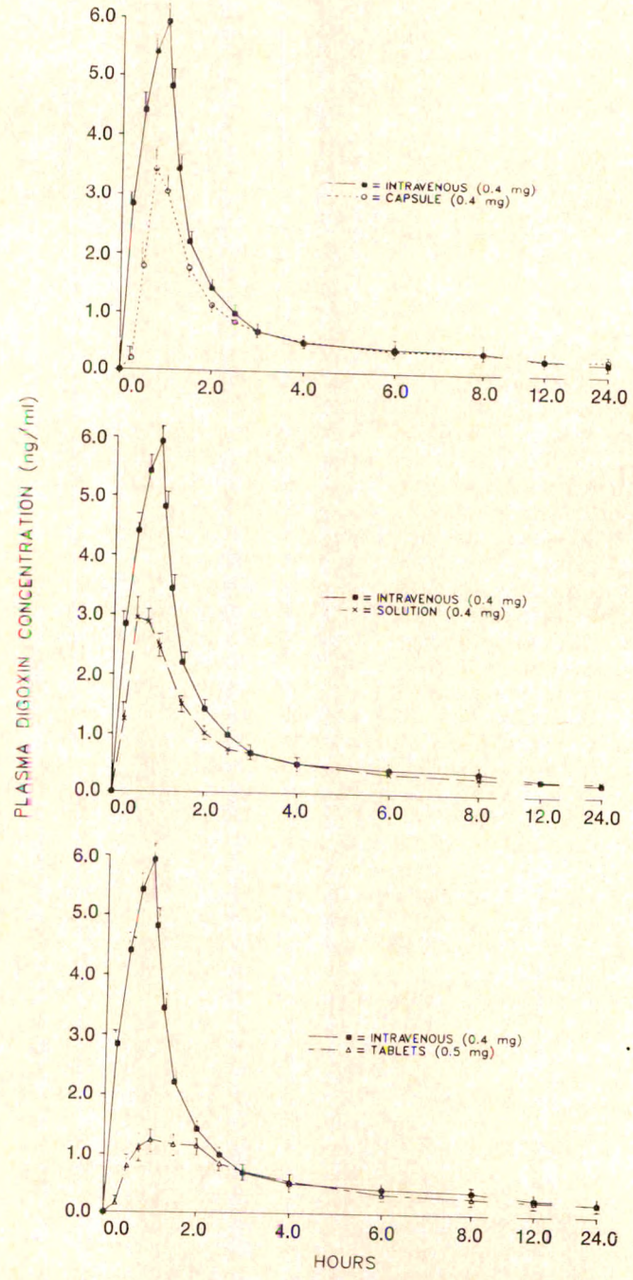


FIGURE 3. Single dose plasma concentration curves for intravenous digoxin in comparison with curves for each of the three oral preparations. Each point is the mean (± standard error) for all 12 subjects at the time shown.

<0.01). The tablet-capsule and tablet-solution differences were significant (P <0.01), whereas solution and capsules were not significantly different.

Pharmacokinetic functions were determined in 8 subjects after ingestion of capsules, 11 subjects after solution and 10 subjects after tablets. One-way analysis of variance indicated an overall difference in apparent lag time before the start of absorption ($F = 5.95$, d.f. = 2,26, P <0.01) although differences between the preparations were small and not likely to be of substantial clinical importance (Table II). Differences in absorption half-life also were significant ($F = 4.24$, d.f. = 2,26, P <0.05); values of $t_{1/2a}$ for capsules and solution were similar (11.3 and 10.2 minutes, respectively), and values for both were smaller than that for tablets (27.1 minutes).

The findings strongly suggest that the rate of digoxin absorption from capsules and solution is very similar. However, digoxin is more slowly absorbed from tablets; peak levels are reached later after dosing, and absorption half-life values are longer. For all three preparations there was a lag time between administration and the start of absorption.

Single dose bioavailability: Analysis of variance indicated a significant difference among preparations in dose-adjusted values of the 24-hour area under the concentration curve ($F = 10.25$, d.f. = 3,33, P <0.01). Systemic availability of all three oral preparations, as judged by comparison of the area under the concentration curve and the intravenous value, was significantly less than 100 percent. Mean 24 hour area under the concentration curve for capsules was 79.2 percent of the intravenous value (P <0.05, Newman-Keuls test); the solution averaged 76.2 percent of the intravenous value (P <0.05), and dose-corrected tablets averaged only 49.5 percent of the intravenous value (P <0.05) (Fig. 2). Figure 3 shows the composite intravenous curve compared with that of each of the oral preparations.

Twenty-four-hour urinary excretion of digoxin after single doses yielded similar findings. The overall difference between the four treatments in 24 hour urinary excretion was highly significant ($F = 36.06$, d.f. = 3,33, P <0.001). An average of 130 mg of digoxin (32.5 percent of the dose) was excreted during 24 hours after intravenous dosage. Excretion after administration of capsules averaged 62.5 percent of the intravenous value (P <0.01); for solution, excretion was 61.8 percent of the intravenous value (P <0.01). Digoxin excretion after ingestion of tablets, when corrected for dose, averaged only 40.9 percent of the intravenous value (P <0.01) (Fig. 2).

The findings indicate that the systemic availability of all oral digoxin preparations was significantly less than 100 percent. The bioavailability of capsules was approximately equivalent to that of the solution, whereas that of the tablet preparation used in this study

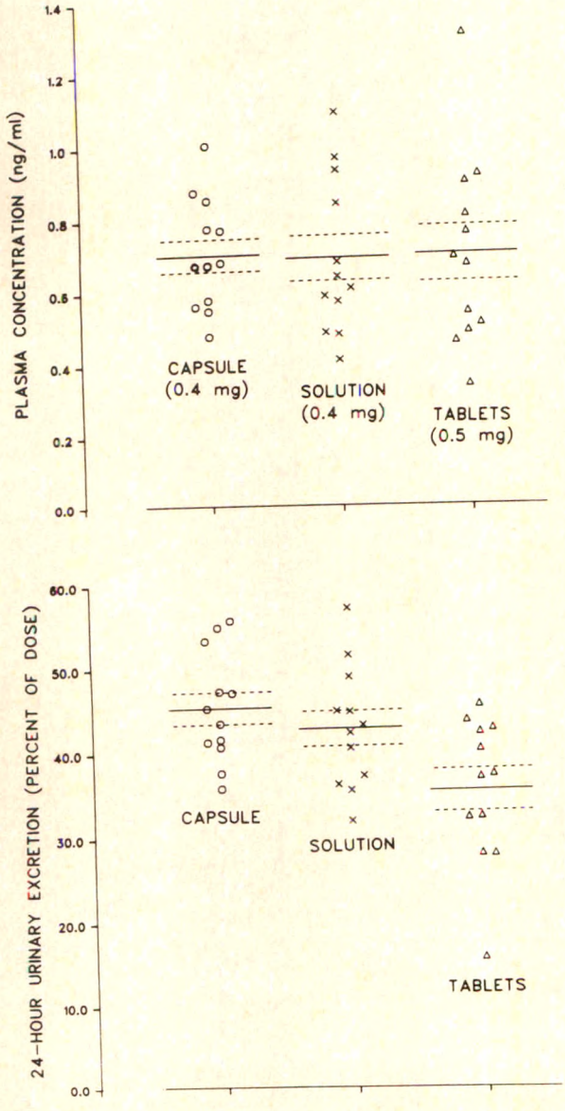
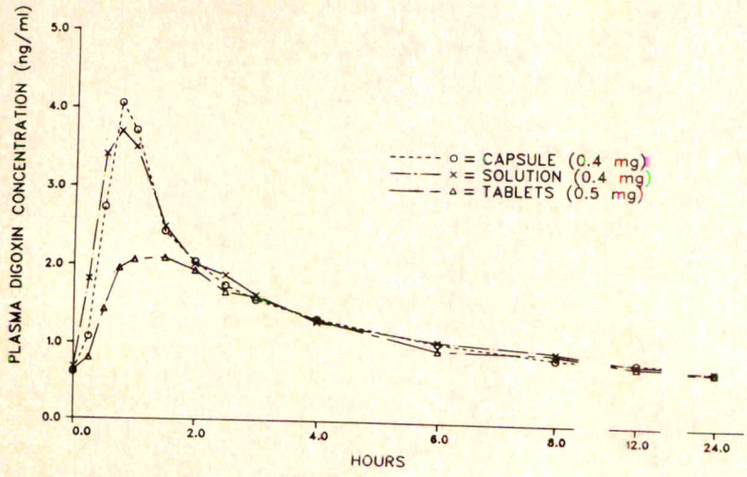


FIGURE 4. Steady state plasma concentrations (**above**) and 24 hour urinary excretion rates (**below**) for the three oral preparations during multiple dose therapy. Each data point is the mean of four to six daily measurements for a given subject. The figure shows the across-subject mean (± standard error) of these individual mean values. The urinary excretion data are expressed as percent of dose, thereby taking into account differences in dosages among the preparations.

TABLE III
Comparison of Within- and Between-Subject Variability in Bioavailability*

Bioavailability Measure	Mode of Administration			
	Intravenous	Capsule	Solution	Tablets
Single dose AUC (between subjects)	28.4	25.9	26.9	45.1
Single dose UE (between subjects)	16.0	18.6	33.6	22.7
Steady state AUC (between subjects)	. . .	28.9	24.8	30.2
Steady state plasma level (pooled within subjects)	. . .	18.7	22.5	20.5
Steady state plasma level (between subjects)	. . .	22.6	31.6	26.3
Steady state UE (pooled within subjects)	. . .	21.6	23.3	19.9
Steady state UE (between subjects)	. . .	14.6	17.1	24.5

* Expressed as coefficient of variation (in percent).
AUC = area under the plasma concentration curve; UE = urinary excretion.



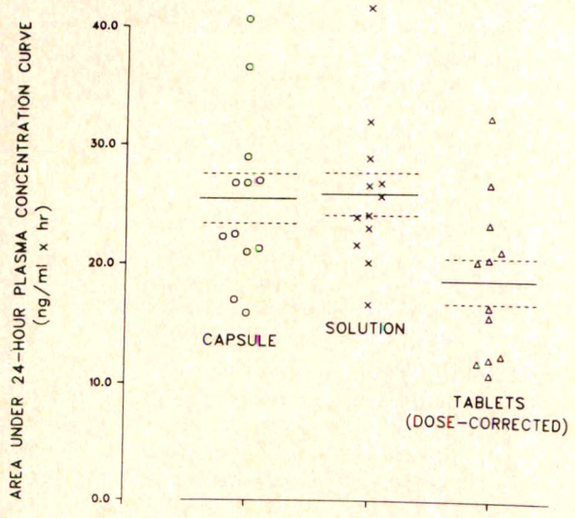


FIGURE 5. Above, plasma digoxin concentration during the final steady state dosage interval. Each point is the mean for all subjects at the times shown. **Below,** area under the 24 hour plasma concentration curve during the final dosage interval at steady state. Individual values and mean (± standard error) for all 12 subjects are shown.

was substantially less than that of either the solution or capsules.

Steady-state bioavailability: Mean steady state serum digoxin concentrations (in ng/ml) based upon four to six measurements in each subject in each treatment condition were: 0.70 for capsules, 0.69 for solution and 0.69 for tablets (Fig. 4). After correction for dose, the overall difference among treatments was significant ($F = 10.04$, d.f. = 2,22, $P < 0.01$). The tablet-solution and tablet-capsule differences were highly significant ($P < 0.01$ for both comparisons), whereas values for capsules and solution were essentially identical. Likewise, 24 hour urinary excretion in the steady state varied significantly among treatments ($F = 8.40$, d.f. = 2,22, $P < 0.01$). Mean values (for percent of the dose) were: 45.1 for capsules, 42.5 for solution and 35.0 for tablets (Fig. 4). Again the capsule-tablet and solution-tablet comparisons yielded highly significant differences ($P < 0.01$), whereas the capsule-solution comparison showed no significant difference.

Figure 5 shows the composite serum concentration curves for all three oral preparations during the steady state dosage interval. The area under the 24 hour concentration curve at steady state, after correction for dose, differed significantly among preparations ($F = 24.75$, d.f. = 2,22, $P < 0.01$). The area under the concentration curve values for capsules and solution was not significantly different, whereas the area for tablets was significantly less than that for capsules and solution ($P < 0.01$) (Fig. 5).

Thus the single dose findings were supported by the multiple dose study, demonstrating that capsules and solution had essentially identical bioavailability, which was superior to that of the standard tablet preparation under study.

Between- and within-subject coefficients of variation: Table III summarizes the coefficients of variation for all modes of treatment. For the two single

dose measures of bioavailability, intravenous digoxin and oral capsules had approximately equal coefficients of variation, which were less than or equal to those of the solution and tablet preparations. For steady state plasma levels and urinary excretion of digoxin, within- and between-subject coefficients of variation for capsules also were less than or equivalent to those of solution and tablets. For all three treatments, between-subject coefficient of variation values for steady state plasma levels were higher than within-subject values. This was also the case for steady state urinary excretion during treatment with tablets. However, within-subject coefficients of variation for urinary excretion during the capsule and solution treatments exceeded between-subject values.

Discussion

All currently available formulations of digoxin used for oral administration (tablets, elixir) are variably and incompletely absorbed from the gastrointestinal tract.[1] One approach to formulation of oral digoxin preparations with improved bioavailability has been the development of gelatin capsules containing a digoxin solution. Studies of these capsules suggest that the bioavailability of this digoxin preparation is greater and more consistent than that of tablets and possibly of oral digoxin solution.[2–8]

As is customary in current studies of digoxin bioavailability,[2,6,8,10] we utilized a slow intravenous infusion as the reference standard for 100 percent systemic availability. Because values for area under the concentration curve and urinary excretion of digoxin after a given intravenous dose are influenced by the rate of infusion,[2,20] our estimates of absolute systemic availability of oral digoxin preparations apply specifically to the 1 hour intravenous infusion standard. On the basis of this reference system, our findings from the single dose study indicate that the systemic availability of the c[illegible]e preparation is significantly less than 100 percent. [illegible]thermore, the rate and completeness of digoxin a[illegible]orption from capsules were essentially identical to those of a standard digoxin solution. This was evident from comparison of values for areas under the plasma concentration curve or 24 hour urinary excretion of digoxin after single doses, as well as from steady state plasma digoxin levels and urinary excretion values on several consecutive days during long-term therapy. Other reports[2,6,8] have suggested that absorption of the capsule preparation approaches 100 percent completeness and is greater than that of even an oral solution. In any case, it is clear that the bioavailability of digoxin capsules exceeds that of a standard reference tablet.[2–8] Finally, one study[21] suggested that between-subject variability in steady state serum digoxin levels was less during treatment with capsules than with tablets. However, our findings and those of most other investigators[2,3,5–8] do not demonstrate a striking or consistent difference among oral preparations in within- or between-subject coefficients of variation of systemic availability after either single or multiple doses.

Peak plasma digoxin levels after ingestion of the various oral preparations tended to be highest with the capsules. Anecdotal reports[22] and other suggestions[23] have associated high peak digoxin levels with the occurrence of transient cardiac arrhythmias, but systematic experimental study has revealed no such associations.[24] The clinical implications of the high peak digoxin concentrations after ingestion of capsules require further study.

Acknowledgement

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References

1. **Greenblatt DJ, Smith TW, Koch-Weser J:** Bioavailability of drugs: the digoxin dilemma. Clin Pharmacokin 1:36–51, 1976
2. **Marcus FI, Dickerson J, Pippin S, et al:** Digoxin bioavailability: formulations and rates of infusions. Clin Pharmacol Ther 20: 253–259, 1976
3. **Ghirardi P, Catenazzo G, Mantero O, et al:** Bioavailability of digoxin in a new soluble pharmaceutical formulation in capsules. J Pharm Sci 66:267–269, 1977
4. **Johnson BF, Smith G, French J:** The comparability of dosage regimens of Lanoxin tablets and lanoxicaps. Br J Clin Pharmacol 4:209–211, 1977
5. **Mallis GI, Schmidt DH, Lindenbaum J:** Superior bioavailability of digoxin solution in capsules. Clin Pharmacol Ther 18:761–768, 1976
6. **Johnson BF, Bye C, Jones G, et al:** A completely absorbed oral preparation of digoxin. Clin Pharmacol Ther 19:746–751, 1976
7. **Lindenbaum J:** Greater bioavailability of digoxin solution in capsules. Clin Pharmacol Ther 21:278–282, 1977
8. **Binnion PF:** A comparison of the bioavailability of digoxin in capsule, tablet, and solution taken orally with intravenous digoxin. J Clin Pharmacol 16:461–467, 1976
9. **Smith TW, Butler VP, Haber E:** Determination of therapeutic and toxic serum concentrations by radioimmunoassay. N Engl J Med 281:1212–1216, 1969
10. **Greenblatt DJ, Duhme DW, Koch-Weser J, et al:** Evaluation of digoxin bioavailability in single-dose studies. N Engl J Med 289: 651–654, 1973
11. **Usanis RA:** NLIN—Nonlinear Least Squares Estimation of Parameters (Library Services Series Document no. LSR-089-1). Research Triangle Park, North Carolina, Triangle Universities Computation Center, 1972
12. **Marquardt DW:** An algorithm for least-squares estimation of nonlinear parameters. J Soc Ind Appl Math 11:431–441, 1963
13. **Greenblatt DJ, Pfeifer HJ, Ochs HR, et al:** Pharmacokinetics of quinidine in humans after intravenous, intramuscular and oral administration. J Pharmacol Exp Ther 202:365–378, 1977
14. **Greenblatt DJ, Koch-Weser J:** Clinical pharmacokinetics. N Engl J Med 293:702–705, 964–970, 1975
15. **Wagner JG:** Fundamentals of Clinical Pharmacokinetics. Hamilton, Illinois, Drug Intelligence Publications, 1975

Three Cases of Hypotension and Syncope With Ventricular Pacing: Possible Role of Atrial Reflexes

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Hypotension with lightheadedness and near syncope occurred in three patients during effective ventricular pacing. Hemodynamic studies demonstrated a decrease in cardiac output ranging from almost no decrease to 15 percent, presumably related to the loss of effective atrial contraction. The decrease in output was too small to explain by itself the reduced blood pressure, which resulted from paradoxic reduction of total peripheral resistance in one patient and from failure of resistance to increase in two. Baroceptor reflexes (Valsalva response) were normal in all three patients; hence it is suggested that the failure of compensatory increases in total peripheral resistance may be due to a reflex from the sudden atrial distension that occurs during atrioventricular (A-V) dissociation. The fluctuations in arterial pressure during ventricular pacing were synchronous with the appearance of cannon waves in the right atrial pressure tracing.

Arterial pressure during A-V dissociation thus appears to be balanced by two opposite reflexes: the baroceptor reflex, which attempts to compensate for reduction in output, and atrial distension, which reduces peripheral resistance.

Apart from its passive transport function, the atrium can play a positive role in improving cardiac performance; this has repeatedly been demonstrated in physiologic studies both in animals[1,2] and in man.[3,4] The clinical translation of these observations has usually been restricted to problems of cardiac decompensation and response to therapy.[5] However, we have encountered another clinical expression of the loss of effective atrial contraction: Significant postural hypotension, ending sometimes in syncope, occurred in some patients when ventricular pacing induced atrioventricular (A-V) dissociation. This decrease in blood pressure led to problems in diagnosis and therapy, and subsequent physiologic investigations suggested that the cause is more complex than a simple reduction in cardiac output.

Material and Methods

Three patients were studied; two (Patients 1 and 2) had syncopal attacks after insertion of a demand ventricular pacemaker for bradyarrhythmia syndrome. The third patient, who also had bradyarrhythmia, was investigated before the insertion of a pacemaker to determine the exact type needed. Hemodynamic studies were performed in a quiet laboratory in the morning after an overnight rest, with the patient fasting and lying comfortably supine. No premedication was used. In all patients, plasma volume was determined first with $RISA^{125}$ using a 10 minute equilibration period, and total blood volume was calculated from the plasma volume and simultaneous hematocrit using appropriate correction factors as previously described.[6] Then cardiac output was determined with the dye-dilution technique (indocyanine green dye)[7] in one patient and the thermodilution technique[8] in the other two. Catheters were introduced percutaneously into an antecubital vein and brachial artery and carefully positioned

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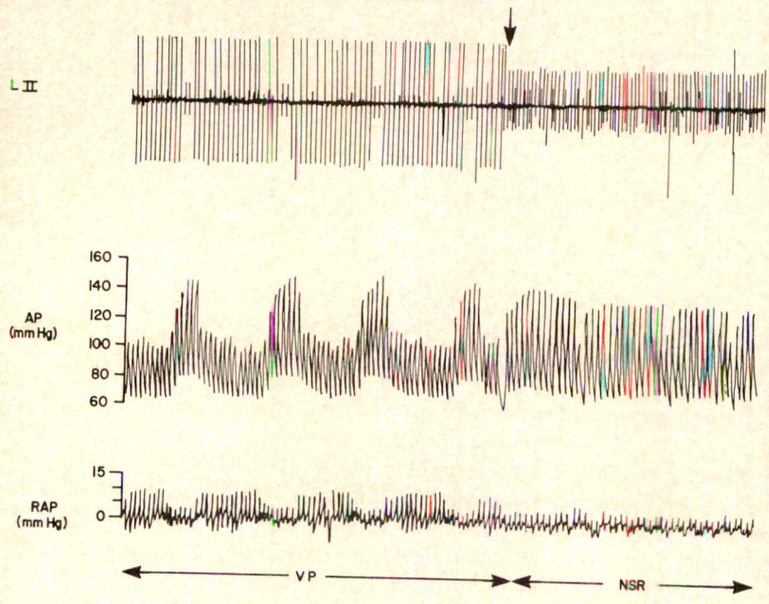

FIGURE 1. Patient 1. Variations in arterial blood pressure coincident with phasic activity of the pacemaker (recorded in lead II [LII]). The activation of the ventricular pacemaker (VP) was associated with cannon waves in the right atrial pressure (RAP) tracing and coincided with phases of low arterial pressure (AP). Inactivation of the pacemaker (↓) by external inhibition and return of normal sinus rhythm (NSR) was associated with the disappearance of cannon waves; the fluctuation in arterial blood pressure ceased, and blood pressure settled at the higher level of the previous fluctuations.

under fluoroscopy. The venous catheter was advanced into the right atrium for the dye-dilution determination and into the pulmonary artery for the thermodilution measurements. The arterial catheter was advanced to the root of the ascending aorta in all patients. Intraarterial pressure, right atrial pressure and electrocardiographic lead II were recorded continuously on photographic paper. Derived values, such as total peripheral resistance, were calculated using classic formulas.[7] In the first two patients heart rate and rhythm were controlled by manipulation of the ventricular pacemaker; in the third patient a temporary pacemaker inserted through the femoral vein at the time of the study was used to pace either the right atrium or the right ventricle.

The Valsalva maneuver was used as a test of baroceptor responses; the patients were instructed to blow against a resistance of 40 mm Hg for 20 seconds. The effectiveness of the maneuver was checked by recording the right atrial pressure, and the sensitivity of the reflex responses was determined by the ratio of diastolic overshoot to the reduction in pulse pressure.[9]

The results obtained were compared with hemodynamic findings in four other patients who had a ventricular pacemaker but did not have hypotension with pacing. All four were studied with the thermodilution technique using the procedure described. None of the seven patients was receiving antihypertensive medication or other form of therapy, except for one control patient who was receiving Dilantin®. Standard statistical methods were used to calculate t tests and probability (P) values of differences.[10]

Results

Patient 1

This was a 52 year old man who presented with lightheadedness and syncopal attacks that persisted after insertion of a ventricular demand pacemaker for hypersensitive carotid sinus. A 24 hour dynamic electrocardiogram (Holter monitor) showed that these attacks did not occur because of transient ventricular arrest or fibrillation or because of episodes of excessive tachycardia or bradycardia. Heart rate was maintained

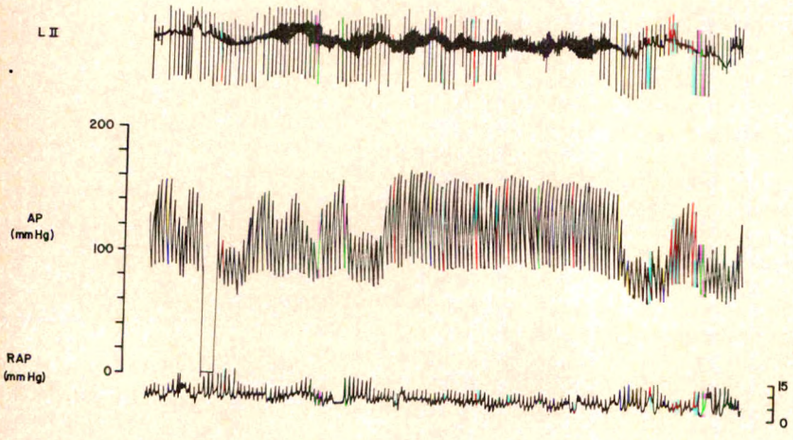

FIGURE 2. Patient 1. Arterial blood pressure fluctuations disappeared when the pacemaker activity was overcome by sinus tachycardia induced by static exercise. Abbreviations as in Figure 1.

TABLE I
Changes in Cardiac Output and Total Peripheral Resistance With Ventricular Pacing

Patient	Rhythm	HR (beats/min)	BP (mm Hg)	Cardiac Output (liters/min)	TPR (dynes·sec·cm^{-5})
1	NSR	62	130/75	4.96	1505
	VP	72	107/60	4.22	1548
2	NSR	80	104/68	6.28	1019
	VP	78	100/65	6.20	989
3	NSR	74	158/90	6.27	1438
	AP	80	168/96	7.03	1365
	VP	85	118/80	6.00	1235

AP = atrial pacing; BP = blood pressure; HR = heart rate; NSR = normal sinus rhythm; TPR = total peripheral resistance; VPS= ventricular pacing.

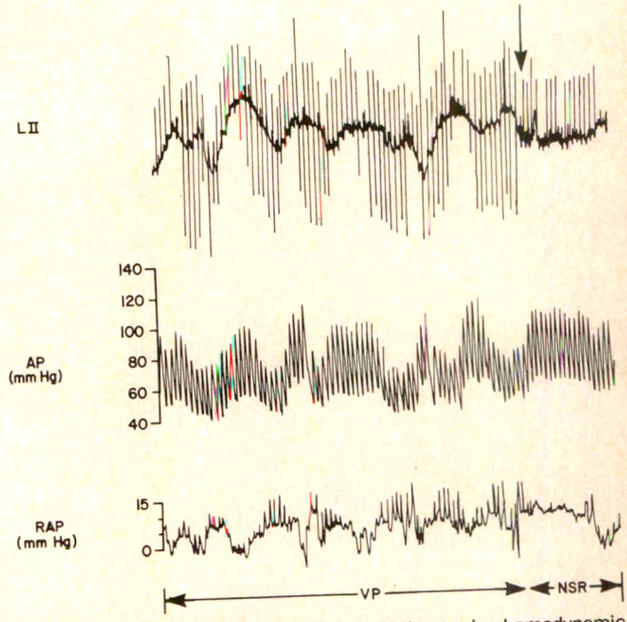

FIGURE 3. Patient 2. Tracings obtained during supine hemodynamic study. Explanation and abbreviations as in Figure 1.

within physiologic limits, but heart rhythm alternated between responses to normal sinus impulses and to right ventricular pacing. Coincident with these alterations from one rhythm to the other, arterial pressure varied widely from 96/64 to 142/82 mm Hg (Fig. 1). These variations were not related to respiration and persisted when the patient held his breath in either inspiration or expiration; they were clearly associated with the phasic activity of the pacemaker.

Arterial and atrial pressure: Activation of the pacemaker (large lead II complexes) (Fig. 1) was associated with cannon waves in the atrial pressure tracing; these waves coincided with phases of low arterial pressure. When the first beat showed a cannon atrial wave, the blood pressure suddenly decreased and then remained at a low level until normal sinus rhythm was reestablished. The arterial pressure fluctuations disappeared when the pacemaker activity was overcome by sinus tachycardia induced either by 1.5 mg atropine administered intravenously or by static exercise (maximal hand grip) (Fig. 2). In addition, when the pacemaker was turned off by external inhibition and cardiac action followed its normal sinus rhythm, all fluctuations in arterial blood pressure disappeared, and the blood pressure settled at the higher level of the previous fluctuations (Fig. 1). The patients received no medication during any of these observations; administration of Valium had been discontinued on hospitalization.

Hemodynamics: Blood volume was moderately contracted (26.5 ml/cm or 86 percent of normal for our laboratory[6]) mainly because of the reduction of plasma volume (14.7 ml/cm or 79 percent of normal.). Hemodynamic studies during normal sinus rhythm demonstrated a low cardiac output and slightly increased total peripheral resistance (normal for our laboratory is 1,360 ± 178 [mean ± standard deviation] dynes·sec·cm^{-5}). The hypotension associated with ventricular pacing occurred despite a higher heart rate and was due to a 14.9 percent reduction in cardiac output with no compensatory increase in total peripheral resistance (Table I).

Patient 2

This 49 year old man had a demand ventricular pacemaker inserted because of bradyarrhythmia. Despite demonstrably effective pacing, he continued to have marked lightheadedness and near fainting, mainly in the upright position. These episodes were not related to transient cardiac arrhythmias, as indicated by a 24 hour dynamic electrocardiogram that showed effective control of heart rate by the ventricular pacemaker. The patient received no medication during this period and was studied while he was still untreated. Blood volume was within normal limits (29.9 ml/cm or 97 percent of normal for our laboratory). Hemodynamic studies were performed while the patient was in the supine and upright positions, during both ventricular pacing and the normal rhythm that developed after external inactivation of the pacemaker.

Hemodynamics during pacing: Ventricular pacing was associated with the expected A-V dissociation and cannon waves in the right atrial pressure tracing (Fig. 3). In the supine position, the shift from normal sinus rhythm to ventricular pacing was associated with only minimal hemodynamic alterations (Table I). However, during repeat studies in the upright position, marked alterations were observed that correlated well with the patient's orthostatic symptoms. During standing, while normal sinus rhythm was maintained, cardiac output decreased as expected, but total peripheral resistance increased and arterial pressure was maintained (104/68 versus 103/79 mm Hg). This normal hemodynamic response to standing[9] differed from the response observed when the ventricular pacemaker was activated in the same upright position. Cardiac output was then further reduced from 4.81 to 3.34 liters/min (Table II), but this reduction did not evoke an increase in peripheral resistance; as a result, arterial pressure decreased from 103/79 to 80/58 mm Hg and the patient complained of lightheadedness.

Patient 3

This 47 year old man had recurrent episodes of dizziness and, occasionally, syncope that were ascribed clinically to paroxysmal bradyarrhythmia. A prospective study of the hemodynamic effects of temporary cardiac pacing (atrial and ventricular) was planned to assess whether an R-triggered or an atrial-driven ventricular pacemaker would be most appropriate for the patient. The patient was taking no medication while the studies were performed; his antihypertensive treatment had been discontinued 2 weeks earlier. Blood vol-

TABLE II
Patient 2. Response of Total Peripheral Resistance to Reduction in Cardiac Output: Contrast Between Standing With Normal Sinus Rhythm and Ventricular Pacing

	Supine	Standing	Standing With VP
Rhythm	NSR	NSR	VP
HR (beats/min)	80	90	78
BP (mm Hg)	104/68	103/79	80/58
CO (liters/min)	6.28	4.81	3.34
TPR (dynes·sec·cm^{-5})	1019	1447	1565

For a reduction of 23.4 percent in cardiac output on standing, total peripheral resistance increased by 42.0 percent, whereas for a larger diminution in output induced by ventricular pacing in the standing position (30.6 percent), total peripheral resistance remained essentially unchanged (+8 percent), so that blood pressure decreased significantly. BP = blood pressure; CO = cardiac output; HR = heart rate; NSR = normal sinus rhythm; TPR = total peripheral resistance; VP = ventricular pacing.

TABLE III
Hemodynamic Changes With Ventricular Pacing (Four Patients With Stable Blood Pressure)

Patient	Rhythm	HR (beats/min)	BP (mm Hg)	Cardiac Output (liters/min)	TPR (dynes·sec·cm^{-5})
1	NSR	57	154/61	3.24	3440
	VP	60	140/64	2.60	4160
2	NSR	66	121/72	5.22	2320
	VP	90	118/82	4.20	3120
3	NSR	60	166/82	6.00	2880
	VP	80	152/85	5.40	3120
4	NSR	86	132/67	6.46	2560
	VP	95	141/80	5.27	3200
Means	NSR	67	143/71	5.23	2800
	VP	81	138/78	4.37	3440
P		NS	NS	<0.01	<0.02

NS = not significant; P = probability; other abbreviations as in Table I.

ume was mildly expanded (35.2 ml/cm or 114 percent of normal) because of a slight increase of red cell mass (16.7 ml/cm; normal for our laboratory 12.2 ± 1.2); plasma volume was normal, 18.5 ml/cm.

Hemodynamics during pacing: Ventricular pacing resulted in a lower cardiac output and arterial pressure than atrial pacing (6.0 liters/min and 118/80 mm Hg versus 7.03 and 168/96, respectively), despite comparable heart rates (85 beats/min with ventricular pacing and 80 during atrial pacing (Table I). A similar association of low arterial pressure with lower cardiac output during ventricular pacing has previously been reported[4]; however the 14.6 percent reduction in output (1.03 liters/min) should normally be compensated for by an increase in peripheral resistance.[11] The decrease in arterial pressure with ventricular pacing was not due to reduction in output alone, as demonstrated by comparison of arterial pressures during normal sinus rhythm (74/min) with those during ventricular pacing (85/min). Although both rhythms were associated with the same level of cardiac output, arterial pressure was much lower during ventricular pacing than during sinus rhythm (118/80 versus 158/90 mm Hg).

Control Patients

The results in these three patients were compared with those obtained in four patients who had a ventricular pacemaker of similar design but no hypotension with pacing. One of these four patients was receiving Dilantin, but the other three were receiving no medication. During ventricular pacing the decrease in cardiac output of 16.9 ± 4.7 percent (mean ± standard deviation) was compensated for by an increase in total peripheral resistance (+22 ± 10.8 percent), so that arterial pressure was unchanged (Table III). The main difference between the groups with and without pacing-induced hypotension was the response of peripheral resistance to the decrease in cardiac output. Cardiac output decreased 13 percent in patients with hypotension (including data from the study performed during standing) 16.9 percent in those without hypotension (difference not significant); in contrast, peripheral resistance was practically unchanged (−1.5 percent) in the group with hypotension but increased 22 percent in the group without hypotension (P <0.02). Blood volume in the latter four patients ranged from a moderate decrease in two (80 percent of normal) to near normal values (90 per cent of normal) in two.

Discussion

Variation of arterial pressure with timing of atrial contraction in relation to ventricular systole has been described before,[4,12–14] but the occurrence of symptomatic hypotension during effective ventricular pacing has not previously been reported in ambulatory patients. As shown in our three patients, syncope or severe lightheadedness, or both, can occur despite adequate ventricular pacing and pose serious diagnostic problems. Our hemodynamic data suggest that the lower arterial pressure responsible for these cerebral symptoms is related to loss of effective atrial contraction and not to changes in cardiac output alone.

Contribution of atrial systole to cardiac output and arterial pressure: Braunwald[12] demonstrated that, in cardiac cycles in which atrial systole is properly timed, values for left ventricular end-diastolic pressure and volume and brachial arterial pressure are higher than in cycles in which ventricular contraction is not preceded by appropriately timed atrial systole. These results were confirmed by many investigators[4,15–17]; the phenomenon was attributed to an increase in the force of left ventricular contraction induced by elevated left ventricular end-diastolic pressure and volume resulting from a well timed "atrial kick."

There is little doubt that ventricular performance is enhanced when the atrial beat properly precedes ventricular contraction but, as Burchell[18] pointed out, the actual contribution of atrial systole to cardiac output is not a fixed value but can vary within wide limits depending on heart rate, myocardial status or valve disease. More importantly, there is no obvious reason why the variation in output that could be attributed to the loss of effective atrial systole should result in a decrease in arterial pressure. A reduction in cardiac output by 25 or 30 percent is well within the potential of normal compensatory reflexes, as shown by hemodynamic studies of head-up tilt[9] or intravenously adminstered propranolol[19] or practolol.[20] Similar observations were also reported with the rapid reduction in cardiac output

that occurs within 20 to 30 minutes after the intravenous administration of furosemide; arterial pressure remained unchanged despite a 17 percent decrease in output.[21] This was also demonstrated in our four asymptomatic patients (Table III): Despite a 10 to 20 percent reduction in cardiac output with ventricular pacing, arterial pressure was unchanged because of the 22 percent increase in peripheral resistance.

Hypotension during ventricular pacing and peripheral resistance: In our three patients whose blood pressure decreased with ventricular pacing, the hypotension was not due to an excessive reduction in output but rather was related to the failure of the normal compensatory response of peripheral resistance. Studies in the upright position clearly illustrated this point. During normal sinus rhythm, total peripheral resistance increased with tilt to compensate for the decrease in cardiac output, whereas it did not change despite a similar output reduction induced by pacing (Table II). This paradoxic lack of total peripheral resistance response could not be related to impaired baroceptor reflexes, because all three patients demonstrated a normal blood pressure response to the Valsalva maneuver. The coincidence of a decrease in arterial pressure during A-V dissociation with the recording of cannon waves in atrial tracings led to the suggestion that the paradoxic behavior of peripheral resistance might be related to an atrial reflex. This suggestion is in agreement with the experimental results of Kahl et al.[22] They found that inflation of a balloon in the left atrium led to a decrease in arterial pressure because the decrease in cardiac output was not compensated for by an increase in peripheral resistance, in contrast, similar decreases in output due to occlusion of the superior vena cava led to fully compensatory increases in total peripheral resistance.

Role of atrial reflexes in cardiovascular control: The atria are known to contain *A* vagal receptors that discharge with the *a* wave of the atrial pressure curve, that is, during atrial contraction.[23] Linden[24] successfully emphasized the role of atrial reflexes in cardiovascular control; of particular importance is his suggestion that atrial receptors are "the first link in a negative feed-back mechanism controlling heart volumes." The reflexes initiated by atrial distension include tachycardia without inotropic stimulation[25] and also increase in urinary flow,[26] but effects on peripheral resistance vary. Although Carswell et al.[27] found no change in total peripheral resistance in the femoral bed of anesthetized dogs, more recent studies suggested a vasodilator effect,[28] at least in the kidneys. Selective electrical stimulation of *A* fibers in cats was shown to produce bradycardia and systemic vasodilation, particularly in the renal vascular bed.[28] They could be stimulated by an increase in atrial pressure whether the pressure was increased by transfusion or by occlusion of the aortic, pulmonary arterial, mitral or tricuspid orifices.[29] Recordati et al.[30] recorded the activity of these receptors from the right cervical vagus nerve in anesthetized cats with normal sinus rhythm when the heart was paced at a fixed rate. Changing the atrial volume by infusion of saline solution, bleeding and occlusion of the inferior vena cava demonstrated that the systolic discharge of the *A* vagal receptors was a function of the active tension developed by atrial muscle during contraction. Our results suggest that when the atrium contracts against a closed valve, a momentary vasodilating reflex could be induced by stimulation of some atrial receptors. In fact, Kahl et al.[22] stressed the predominance of reflexes initiated by these atrial receptors over those of the arterial baroceptors.

Implications: Improperly timed atrial contractions can lead to different hemodynamic effects, depending on their influence on cardiac output and on the reflexes generated. In most cases ventricular pacing will reduce cardiac output, but the blood pressure response will depend on the ability to compensate for that reduction. Two opposing reflexes are important: (1) a vasoconstrictive reflex to the reduction in arterial pressure and cardiac output, and (2) a vasodilator reflex resulting from stimulation of the atrial *A* vagal receptors. Because of the multiplicity of factors, it is not surprising to note the wide range of clinical manifestations in patients with spontaneous or pacemaker-induced A-V dissociation. The hemodynamic changes with ventricular pacing may balance each other so as to produce no symptoms in the majority of patients; however, in a few the tendency for arterial pressure to decrease may predominate. Lightheadedness or syncope will then occur either at rest or with some added stress such as standing up.

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References

1. **Gilmore JP, Sarnoff SJ, Mitchell JH, et al:** Synchronicity of ventricular contraction: observations comparing hemodynamic effects of atrial and ventricular pacing. Br Heart J 25:299–307, 1963
2. **Finney JO Jr:** Hemodynamic alterations in left ventricular function consequent to ventricular pacing. Am J Physiol 208:275–282, 1965
3. **Samet P, Bernstein WH, Nathan DA, et al:** Atrial contribution to cardiac output in complete heart block. Am J Cardiol 16:1–10, 1965
4. **Martin RH, Cobb LA:** Observations on the effect of atrial systole in man. J Lab Clin Med 68:224–232, 1966
5. **Braunwald E, Frahm CJ:** Studies on Starling's law of the heart. IV. Observation of the hemodynamic functions of the left atrium in man. Circulation 24:633–642, 1961
6. **Tarazi RC, Dustan HP, Frohlich ED:** Relation of plasma to interstitial fluid volume in essential hypertension. Circulation 40: 357–365, 1969
7. **Frohlich ED, Tarazi RC, Dustan HP:** Re-examination of the he-

modynamics of hypertension. Am J Med Sci 257:9–23, 1969
8. **Ganz W, Donoso R, Marcus HS, et al:** A new technique for measurement of cardiac output by thermodilution in man. Am J Cardiol 27: 392–396, 1971
9. **Tarazi RC, Dustan HP:** Neurogenic participation in essential and renovascular hypertension, assessed by acute ganglionic blockade. Clin Sci 44:197–212, 1973
10. **Croxton FE, Cowden DJ:** Applied General Statistics. New York, Prentice-Hall, 1944, p 327, 347, 653
11. **Frohlich ED, Tarazi RC, Ulrych M, et al:** Tilt test for investigating a neural component in hypertension. Its correlation with clinical characteristics. Circulation 36: 387–393, 1967
12. **Braunwald E:** Symposium on cardiac arrhythmias. Introduction. With comments on the hemodynamic significance of atrial systole. Am J Med 37:665–669, 1964
13. **Carleton RA, Graettinger JS:** The hemodynamic role of the atria with and without mitral stenosis. Am J Med 42:532–538, 1967
14. **Levy MN, Edelstein J:** The mechanism of synchronization in isorhythmic A-V dissociation. II. Clinical studies. Circulation 42: 689–699, 1970
15. **Valero A:** Atrial transport dysfunction in acute myocardial infarction. Am J Cardiol 16:22–30, 1965
16. **Snell RE, Luchsinger PC, Shugoll GI:** The relationship between the timing of atrial systole and the useful work of the left ventricle in man. Am Heart J 72:653–658, 1966
17. **Snyder JH, Bender F, Kitchin AH, et al:** Atrial contribution to stroke volume in dogs with chronic heart block. Circ Res 19:33–41, 1966
18. **Burchell HB:** A clinical appraisal of atrial transport function. Lancet 1:775–779, 1964
19. **Ulrych M, Frohlich ED, Dustan HP, et al:** Immediate hemodynamic effects of beta-adrenergic blockade with propranolol in normotensive and hypertensive man. Circulation 37:411–416, 1968
20. **Niarchos AP, Tarazi RC:** Hemodynamic effects of β-adrenergic blocking agents in hypertension. In, Regulation of Blood Pressure by the Central Nervous System (Onesti G, Fernandes M, Kim KE, ed). New York, Grune & Stratton, 1976, p 397–409
21. **Tarazi RC, Dustan HP:** Hemodynamic effects of diuretics in hypertension. Contrib Nephrology 8:162–170, 1977
22. **Kahl FR, Flint JF, Szidon JP:** Influence of left atrial distention on renal vasomotor tone. Am J Physiol 226:240–246, 1974
23. **Arndt JO, Brambring R, Hindorf K, et al:** The afferent discharge pattern of atrial mechanoreceptors in the cat during sinusoidal stretch of atrial strips *in situ*. J Physiol 240:33–52, 1974
24. **Linden RJ:** Function of nerves of the heart. Cardiovasc Res 6: 605–626, 1972
25. **Furnival CM, Linden RJ, Snow HM:** Reflex effects on the heart of stimulating left atrial receptors. J Physiol 218:447–463, 1971
26. **Ledsome JR, Linden RJ:** The role of left atrial receptors in the diuretic response to left atrial distension. J Physiol 198:487–503, 1968
27. **Carswell F, Hainsworth R, Ledsome JR:** The effects of distension of the pulmonary vein-atrial junctions upon peripheral vascular resistance. J Physiol 207:1–14, 1970
28. **Oberg B, Thoren P:** Circulatory responses to stimulation of medullated and nonmedullated afferents in the cardiac nerve in the cat. Acta Physiol Scand 87:121–132, 1973
29. **Thoren PN:** Atrial receptors with nonmedullated vagal afferents in the cat. Circ Res 38:357–362, 1976
30. **Recordati G, Lombardi F, Bishop VS, et al:** Mechanical stimuli exciting type A atrial vagal receptors in the cat. Circ Res 38: 397–403, 1976

Cardiac Sarcoidosis

Diagnosis With Endomyocardial Biopsy and Treatment With Corticosteroids

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A 27 year old woman was hospitalized for progressive dyspnea, fatigue and retrosternal chest pain. She had progressive cardiac enlargement with clinical and laboratory confirmation of a dilated cardiomyopathy. Transvenous percutaneous right ventricular endomyocardial biopsy yielded a specimen showing a noncaseating granuloma. The patient's dyspnea responded dramatically to steroid therapy with corresponding improvement in radiographic and echographic measures of ventricular performance. This case illustrates the problem of diagnosing cardiac sarcoidosis when there is no apparent evidence of other organ involvement.

Sarcoidosis is a systemic disease that can involve the heart. Although its primary manifestations are pulmonary, it can be an unsuspected cause of cardiac conduction disturbances or severe cardiomyopathy in young adults. In the absence of more obvious pulmonary or lymphatic involvement, the diagnosis may be overlooked in a situation of potentially treatable cardiac disease. We report on a patient with cardiomyopathy secondary to sarcoidosis, diagnosed with percutaneous transvenous endomyocardial biopsy, who exhibited a beneficial response to treatment with corticosteroids.

Case Report

A 27 year old black housewife was transferred to Stanford Medical Center for evaluation of severe cardiomyopathy. She had had an uneventful pregnancy 11 months earlier. There was no history of familial heart disease, tuberculosis, rheumatic fever, hypertension or alcohol abuse. She denied fever, arthralgias and skin lesions. Five months before admission she experienced progressive dyspnea, fatigue and retrosternal chest pain. Evaluation at another hospital included chest roentgenograms and echocardiograms that showed multichamber cardiac enlargement. Results of thyroid, immunologic and infectious disease studies were normal or negative.

Right and left heart catheterization revealed no intracardiac shunt. Coronary arteriography revealed normal coronary arteries. The left ventriculogram showed severe diffuse hypokinesia. The cardiac index was 1.2 liters/min per m^2, and the ejection fraction was 15 percent. Pressures, in mm Hg, were as follows: right atrial mean 16, with an *A* wave of 20 and a *V* wave of 17; pulmonary arterial 51/25 (mean 37); right ventricular end-diastolic 15; pulmonary wedge mean 29; and left ventricular pressure 95 systolic (end-diastolic value 32). The patient's condition did not improve with bed rest or diuretic therapy, and she was limited to constant bed rest.

On physical examination, the patient was a somnolent thin young black woman. The blood pressure was 86/70 mm Hg without pulsus paradoxus, pulse rate 118 beats/min, respiration 20/min and temperature 37° C. There were no skin lesions, peripheral clubbing or edema or lymphadenopathy. The carotid upstroke was normal. The chest was clear to auscultation. A diffuse left ventricular impulse was visible. The first and second heart sounds were normal. A grade 2/6 pansystolic apical murmur and third and fourth sound gallops were

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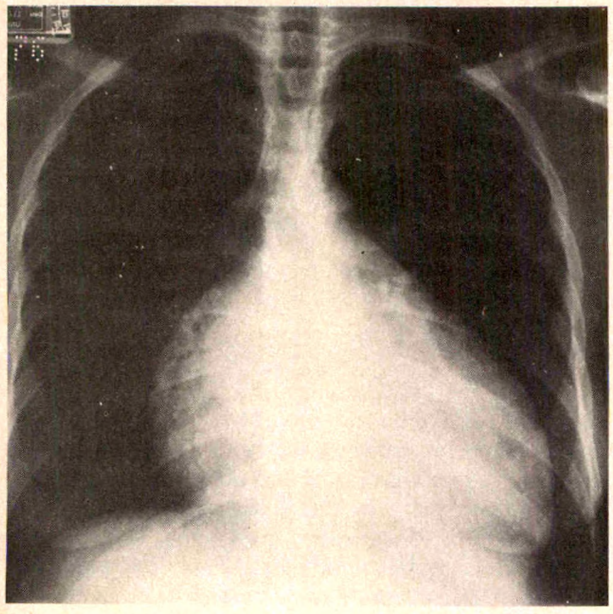

FIGURE 1. The upright posteroanterior chest roentgenogram obtained before administration of specific therapy shows clear lung fields and massive cardiomegaly that partially obscures the hilar areas.

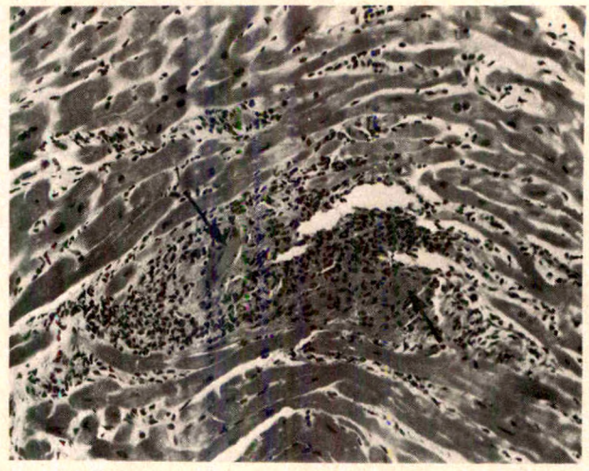

FIGURE 2. Section of endomyocardial biopsy specimen showing a granulomatous lesion with giant cells (**arrows**) and a predominantly lymphocytic infiltrate. (Hematoxylin–eosin ×190, reduced by 28 percent.)

heard. The liver measured 14 cm in vertical span and was tender but nonpulsatile on palpation. The limbs were cool, with intact pulses.

The hemogram and electrolyte determinations were normal. Serum calcium was 9.7 mg/100 ml, serum creatinine 1.0 mg/100 ml, total bilirubin 2.1 mg/100 ml and serum glutamic oxaloacetic transaminase was 80 IU/liter. The serum gamma M globulin was increased to 340 mg/100 ml (normal 60 to 280). Skin tests for mumps, dermatophyton, tuberculosis and coccidiomycosis were nonreactive.

The chest roentgenogram (Fig. 1) showed clear lung fields and massive cardiomegaly. The hila were obscured by the enlarged heart. The electrocardiogram revealed normal sinus rhythm, a QRS axis of 10° and absent R waves in leads V_1 to V_3 with T wave inversion in the inferolateral leads.

The echocardiogram revealed left ventricular enlargement, and the percent fractional shortening (the difference between the end-systolic and end-diastolic diameters divided by the end-diastolic diameter) was 4 percent (normal value greater than 25 percent).

Treatment with thiazide diuretic agents, digoxin and bed rest was continued without improvement. A trial of nitroglycerin ointment with Swan-Ganz catheter monitoring was instituted. Afterload reduction resulted in an increase in cardiac output from 1.8 to 3.7 liters/min, a decrease in pulmonary end-diastolic pressure from 27 to 18 mm Hg, a decrease in pulse rate from 110 to 93 beats/min and an increase in blood pressure from 90/70 to 98/74 mm Hg. The patient's mental status dramatically improved as cardiac output increased. Treatment was continued with nitroglycerin ointment applied every 4 hours. During a 5 day period, she remained alert, her functional status improved and she manifested loss of chest pain, resolution of liver function abnormalities and ability to walk without dyspnea.

A transvenous percutaneous endomyocardial biopsy was performed on the third hospital day. Multiple serial specimens were obtained with a 9.0 French flexible catheter bioptome 50 cm in length. The bioptome had cutting jaws operating on a single-hinge mechanism and was capable of taking samples averaging 2 to 4 mm in diameter.[1] It was passed by way of the right internal jugular vein into the right ventricular apex. One specimen showed a noncaseating granuloma with giant cells and fibrosis (Fig. 2). Cultures of cardiac tissue, urine, sputum and bone marrow revealed no tuberculosis or fungal infection. Results of serologic studies for coccidiomycosis and histoplasmosis were negative. Percutaneous liver biopsy revealed normal findings. Mild hilar adenopathy was obscured in the initial chest roentgenogram because of the cardiomegaly, but became evident with subsequent cardiac shrinkage.

A clinical diagnosis of sarcoidosis was made, based primarily on the presence of a noncaseating granuloma in the myocardium in a young black woman, in the absence of fungal or tuberculous infection. Treatment with prednisone, 20 mg three times daily, was therefore instituted.

Since discharge, the patient has shown gradual but steady improvement over a period of 4 months and has been able to resume normal housework activities and care for her children. The regimen of prednisone, initiated at 60 mg/day, was maintained in excess of 20 mg/day for 2 months, tapered over 5 months and then discontinued after a total corticosteroid course of 7 months. Application of nitroglycerin ointment was discontinued 8 weeks after initiation of prednisone therapy and use of diuretic medications was tapered and discontinued 6 months after initiation of prednisone therapy. Echographic and radiographic indexes of left ventricular function (Fig. 3, Table I) showed rapid improvement during the first month of corticosteroid therapy.

Discussion

Classicially, sarcoidosis presents as a syndrome of acute febrile illness with arthralgias and erythema nodosum, or as a pulmonary disease with bilateral hilar adenopathy that may progress to infiltrates and fibrosis.[2] It is a disease of young adults, and has been reported worldwide. It is characterized by epithelioid granulomatosis without caseation, accompanied by

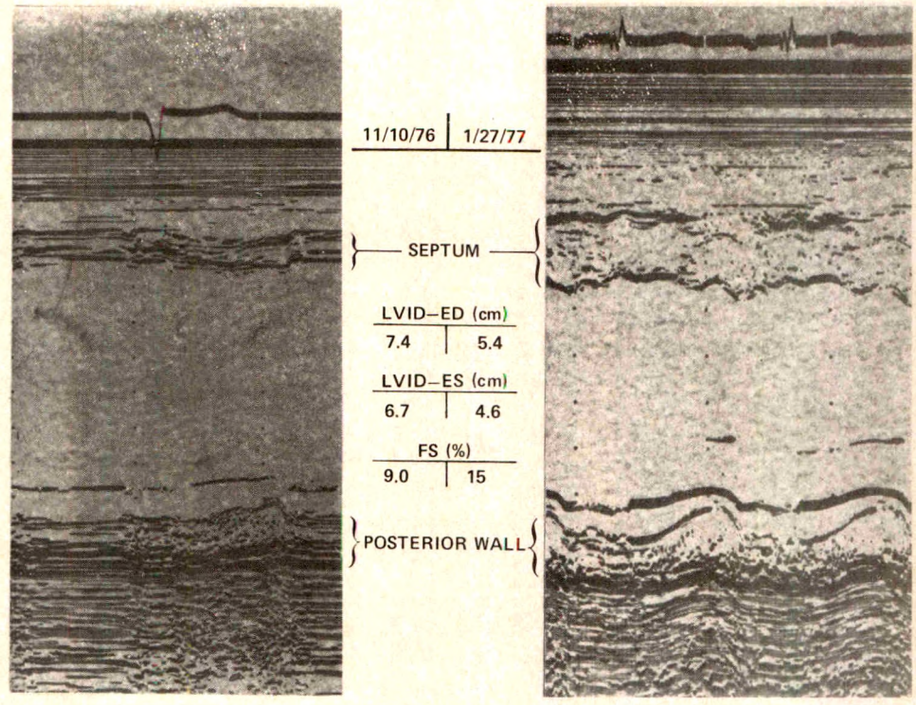

FIGURE 3. Left ventricular echograms before (left) and after (right) treatment with prednisone and nitrites show a decrease in left ventricular internal dimensions (LVID) at end-diastole (ED) and at end-systole (ES) and improved fractional shortening (FS%).

TABLE 1

Effects of Treatment

	1976				1977			
	11/5	11/10	11/12	11/29	12/13	1/27	2/24	6/2
Prednisone (mg/day)	–	–	60	40	40	10	5	0
Nitroglycerin ointment	–	+	+	+	+	–	–	–
FS (%)	4	9	. . .	11	18	15	16	18
$LVID_{ED}$	6.5	7.4	. . .	7.0	5.4	5.4	6.1	6.3
CT ratio	. . .	0.68	. . .	. . .	0.56	0.57	0.57	. . .

– = drug not given; + = drug administered; . . . = data not obtained; CT ratio = cardiothoracic ratio (X-ray examination); FS = fractional shortening (echocardiogram); $LVID_{ED}$ = left ventricular internal dimension at end-diastole (echocardiogram).

chronic inflammatory infiltrate in multiple organs. This process may resolve or progress to fibrosis.

Clinical features: Cardiac sarcoidosis presents with electrocardiographic abnormalities, cardiomyopathy or sudden death. Electrocardiographic abnormalities include heart block, other conduction disturbances, arrhythmias, repolarization disturbances and loss of R wave voltage mimicking myocardial infarction.[3–6] Stein et al.[7] prospectively surveyed the electrocardiograms of 80 young patients with known sarcoidosis and no history of cardiac complaints. They found that 41 patients had abnormal records, including evidence of conduction defects, abnormal repolarization and arrhythmias.

The incidence of clinical congestive heart failure in sarcoidosis, other than that secondary to cor pulmonale, is not known. In autopsy series confined to patients with cardiac sarcoidosis, the incidence rate of congestive heart failure ranged from 23 to 50 percent.[3,4,8–11] In these studies, the incidence rate of sudden death ranged from 16 to 67 percent. In the series of Gozo et al.,[4] the mean age of death secondary to cardiac sarcoidosis was 40 years. Patients in the series of Roberts et al.[10] who presented with cardiac complaints as the principal manifestation of sarcoidosis had little evidence of clinical involvement of other organ systems, as was the case with our patient. In their report, the duration of symptoms before death was usually less than 12 months, and the diagnosis was rarely made before death. Matsui et al.[11] reported that the diagnosis was established during life in only 5 of 42 patients with fatal myocardial sarcoidosis.

Cardiac involvement: Sarcoidosis is estimated to involve the heart in approximately 20 percent of au-

topsy cases of systemic sarcoidosis.[12–14] Noncaseating granulomas and focal or diffuse fibrosis have been reported to involve the myocardium; the conduction system, including the atrioventricular node, His bundle and bundle branches[9]; the papillary muscles[15]; the aortic valve[8]; the mitral valve[4]; and the pericardium.[16] The formation of ventricular aneurysms secondary to extensive scarring has also been reported.[8,9] In the series of Roberts et al.,[10] the left ventricular papillary musculature and upper ventricular septum were the most common sites of involvement. Most reports of cardiac sarcoidosis were based on autopsy series and stressed a grave prognosis and short clinical course; the natural history of the condition is not known.

Diagnosis of cardiac sarcoidosis: Our patient illustrates the problem of correctly diagnosing cardiac sarcoidosis when there is no apparent evidence of other organ involvement. The histologic diagnosis of this disease is usually made in other organs but, when the heart is the primary site of involvement, the diagnosis is usually made at the time of autopsy. Our case is distinctive because the diagnosis of sarcoidosis was established with percutaneous endomyocardial biopsy; it suggests another potentially treatable cause of cardiomyopathy that can be identified with cardiac biopsy. Percutaneous endomyocardial biopsy has been shown to be a safe and informative method of establishing a specific diagnosis in myocardial disease states.[17,18] The finding of the intact noncaseating granuloma may be a result of fortuitous sampling but has been observed in one other case.[11,17] In patients in whom the disease is strongly suspected, obtaining multiple biopsy specimens (three to four samples is our common practice) may increase the diagnostic specificity of the procedure.

Corticosteroid therapy: The administration of prednisone, one of several therapeutic interventions in our patient, probably accounts for her rapid and sustained hemodynamic improvement. Although preload and afterload reduction with nitroglycerin and other agents partially alleviated symptoms of severe left ventricular failure, the persistence of the patient's improved status despite discontinuation of these medications suggests that corticosteroids exerted a beneficial effect. Although steroid administration is advised by most authorities when sarcoidosis involves the heart, eyes and other critical organs, the role of corticosteroid therapy in altering the natural course of cardiac sarcoidosis has not been clearly demonstrated.[2,19]

Stein et al.[20] followed up 15 patients with a diagnosis of probable cardiac sarcoidosis based on organ biopsy or Kveim test positivity. Prednisone in combination with quinidine seemed effective for patients with ventricular arrhythmias as the primary manifestation of their cardiac sarcoidosis. The few patients with congestive heart failure and cardiomegaly did not respond as well, and two deaths in the series resulted from congestive failure.

In summary, our patient's course emphasizes that sarcoidosis should be suspected in young adults, particularly if they are black, with cardiomyopathy, conduction disturbances or other electrocardiographic abnormalities. Clinical deterioration may be rapid and the diagnosis obscured by apparent lack of sarcoidosis in other organs. The use of percutaneous transvenous endomyocardial biopsy may aid the diagnosis of cardiac sarcoidosis and thus permit the initiation of therapy with corticosteroids.

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References

1. **Caves PK, Schulz WP, Dong E Jr, et al:** New instrument for transvenous cardiac biopsy. Am J Cardiol 33:264–267, 1974
2. **Mitchell DN, Scadding JC:** Sarcoidosis. Am Rev Respir Dis 110:774–802, 1974
3. **Porter G:** Sarcoid heart disease. N Engl J Med 263:1350–1357, 1960
4. **Gozo EG, Cosnow I, Cohen HC, et al:** The heart in sarcoidosis. Chest 60:379–388, 1971
5. **Lie JT, Hunt D, Valentine PA:** Sudden death from cardiac sarcoidosis with involvement of the conduction system. Am J Med Sci 267:123–128, 1974
6. **Mikhail JR, Mitchell DN, Ball KP:** Electrocardiographic abnormalities found in patients with sarcoidosis. In, Proceedings of the Sixth International Conference on Sarcoidosis (Iwai K, Hosudo Y, ed). Tokyo, University of Tokyo, 1974, p 365
7. **Stein E, Jackler I, Stimmel B, et al:** Asymptomatic electrocardiographic alterations in sarcoidosis. Am Heart J 86:474–477, 1973
8. **Ghosh P, Fleming HA, Gresham GA, et al:** Myocardial sarcoidosis. Br Heart J 34:769–773, 1972
9. **Morales AR, Levy S, Davis J, et al:** Sarcoidosis and the heart. Pathol Annu 9:139–155, 1974
10. **Roberts WC, McAllister HA, Ferrans VJ:** Sarcoidosis of the heart: Clinicopathologic study of 35 necropsy patients (group I) and review of 78 previously described necropsy patients (group II). Am J Med 63:86–108, 1977
11. **Matsui Y, Iwai K, Tachibana T, et al:** Clinicopathological study on fatal myocardial sarcoidosis. Ann NY Acad Sci 278:455–469, 1976
12. **Longcope WT, Freiman DG:** A study of sarcoidosis. Medicine 31:1–132, 1952
13. **Peacock R, Lippschultz EJ, Lukas A:** Myocardial sarcoidosis. Circulation 16:67–71, 1957
14. **Bashour FA, McConnell T, Skinner W:** Myocardial sarcoidosis. Chest 53:413–420, 1968
15. **Zoneraich S, Gupta MP, Mehta J:** Myocardial sarcoidosis presenting as acute mitral insufficiency. Chest 66:452–454, 1974
16. **Schiff AD, Blatt CJ, Colp C:** Recurrent pericardial effusions secondary to sarcoidosis of the pericardium. N Engl J Med 281: 141–143, 1969
17. **Sekiguchi M, Konno S:** Histopathological differentiation employing endomyocardial biopsy in the clinical assessment of primary myocardial disease. Jpn Heart J 10:30–46, 1969
18. **Mason JW, Billingham ME, Rider AK, et al:** Myocardial biopsy. In, Clinical Cardiology (Willerson JT, Sanders C, ed). In, Science and Practice of Clinical Medicine, Vol 3 (Sanford J, ed). New York, Grune & Stratton, 1977, p 606–613
19. **Siltzbach LE, James DG, Neville E, et al:** Course and prognosis of sarcoidosis around the world. Am J Med 57:847–852, 1974
20. **Stein E, Stimmel B, Siltzbach LE:** Clinical course of cardiac sarcoidosis. Ann NY Acad Sci 278:470–474, 1976

Lack of Connection Between the Atria and the Peripheral Conduction System in a Case of Corrected Transposition With Congenital Atrioventricular Block

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This is the first documented histologic study of the heart of a patient with corrected transposition of the great vessels and congenital atrioventricular (A-V) block with no connection between the atria and an anterior type of peripheral conduction system. Musculature in the superior (anterior) walls of both atria was absent, as was the anterior A-V node. The peripheral conduction system began with the bundle of His. In place of the absent atrial musculature, fibrosis and calcification were present. The relation of laboratory evidence of connective tissue dyscrasia in the mother to the congenital A-V block in the child is discussed.

Although atrioventricular (A-V) block is frequently seen in patients with corrected transposition of the great vessels,[1–13] few histologic studies of the conduction system in this entity have been performed to determine the pathogenesis of the block.[14–16] This report describes the conduction system in such a case with mixed (discordant) levocardia (situs solitus atria with *l*-loop) and A-V block, documenting the first case in which lack of connection of the atria with the peripheral conduction system is a cause of complete A-V block in an anterior type of conduction system. This case is of special interest in that the mother of the child had laboratory evidence of possible connective tissue disease.

Case History*

Twin A: This was the first of premature twins born to a 33 year old (gravida III, para II, abortus 0) white woman on July 14, 1975, after a 34 week gestation period. In January 1975 the mother received doxylamine succinate, pyridoxine hydrochloride, meclizine hydrochloride and medroxy progesterone acetate for a short time, and in March she was given amphetamine to decrease her appetite. Except for the prematurity of the birth, the pregnancy was uneventful. Twins were delivered with a placenta in which both cords had three vessels and which appeared to be a monochorionic diamniotic placenta. The mother had no symptoms of connective tissue disease but did have a positive rheumatoid factor, both latex and human cell titer, with a normal antinuclear antibody pattern.

Physical examination on the first day of life revealed a white female infant weighing 1,630 g in mild respiratory distress; heart rate was 58 beats/min, respiratory rate 80 breaths/min and systolic blood pressure in the arm 70 mm Hg. The heart rate was slow and regular, with a grade 2/6 systolic ejection murmur at the apex and fourth left intercostal space. The limbs were mildly cyanotic and leg pulses weak.

Blood studies showed: Hemoglobin 8.1 g/100 ml, hematocrit 24.8 percent, bilirubin 2 mg/100 ml and blood sugar 120 mg/100 ml. The chest roentgenogram revealed poor aeration of the upper lobes of the lungs and recurrent and shifting atelectasis. The heart was enlarged, and the electrocardiogram disclosed complete A-V block with a narrow QRS configuration (Fig. 1).

The infant was treated for prematurity with intravenous feedings and later hyperalimentation. The anemia was considered secondary to the twin maternal transfusion in utero, and after transfusion the hematocrit increased to 57 percent. Respiratory distress was treated with oxygen and mechanical ventilation.

* This case was briefly described clinically by McCue et al.[17]

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The clinical diagnosis was complex congenital heart disease, probable corrected transposition of the great arteries with pulmonary stenosis and congenital complete heart block. Runs of paroxysmal ventricular tachycardia were initially treated with lidocaine, but multiple premature ventricular complexes continued. Cardiac failure developed and persisted in spite of treatment with digoxin and furosemide. The infant also had runs of severe bradycardia. On July 17, 1975 (at age 3 days), a transvenous temporary pacemaker was inserted, which initially functioned well but then became less efficient as the result of perforation of the anterior ventricular myocardium without tamponade. Later that day, a permanent

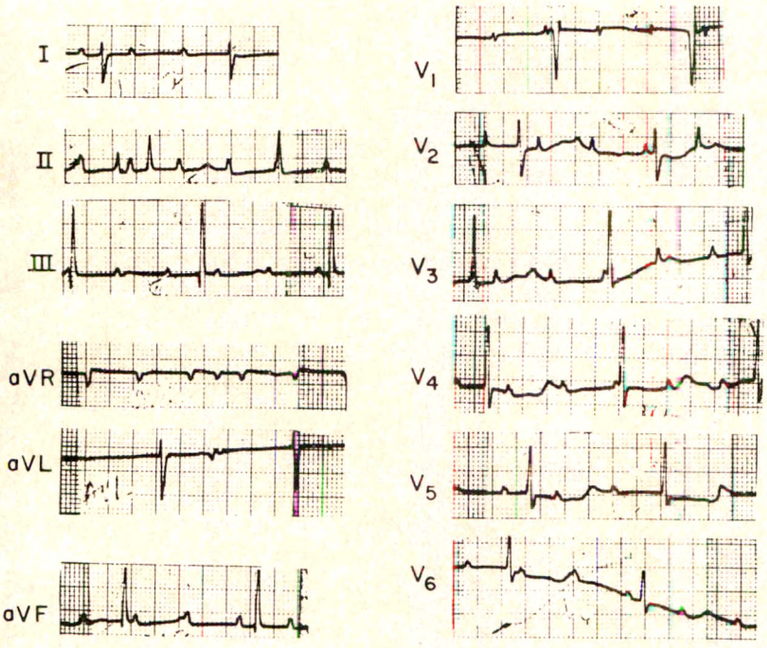

FIGURE 1. Electrocardiogram revealing complete A-V block with an atrial rate of 136/min, a ventricular rate of 54/min, a QRS duration of 0.05 sec, a QR pattern in lead V_1, right atrial enlargement and right ventricular hypertrophy.

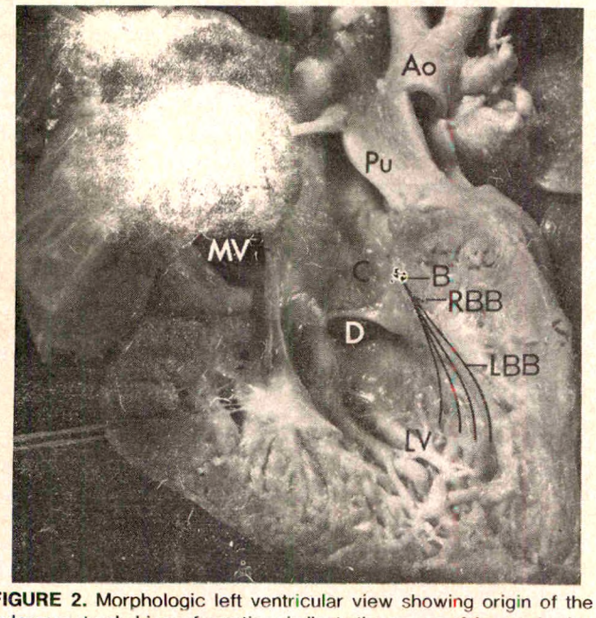

FIGURE 2. Morphologic left ventricular view showing origin of the pulmonary trunk. Linear formations indicate the course of the conduction system. Ao = ascending aorta; B = A-V bundle; C = endocardial curtain; D = ventricular septal defect; LBB = left bundle branch; LV = morphologic left ventricle; MV = mitral valve; Pu = pulmonary trunk; RBB = right bundle branch.

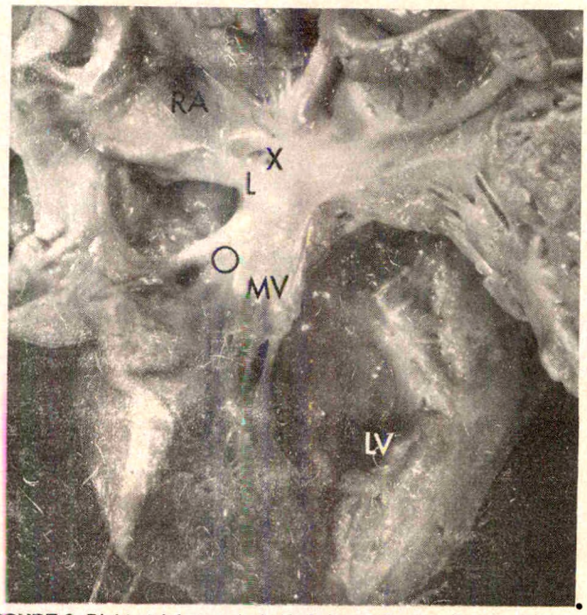

FIGURE 3. Right atrial–morphologic left ventricular view. L = limbus fossae ovalis; LV = morphologic left ventricle; MV = mitral valve; O = approximate area where a posterior A-V node may be found in mixed levocardia with ventricular inversion; RA = right atrium; X = approximate area where the anterior A-V node is expected to be found in mixed levocardia with ventricular inversion.

Medtronic demand pacemaker was installed and appeared to be functioning well, but the infant remained cyanotic and in severe resistant heart failure. She died on July 29, 1975.

Twin B: The second twin weighed 2,100 g and, although she had a grade 2/6 systolic ejection murmur at the left sternal border, she had no cyanosis or distress. The chest roentgenogram showed minimal cardiomegaly with normal pulmonary vasculature, and the electrocardiogram demonstrated congenital complete heart block with a mild left ventricular predominance, a precordial lead pattern very different from her sister's. Heart failure never developed, and the ventricular and atrial rates of 52 and 150/min, respectively, were well tolerated. The echocardiogram disclosed a thick interventricular septum. At age 10 months cardiac catheterization and cineangiocardiography revealed poor contractility of the left ventricle, mild mitral regurgitation and a patent foramen ovale. The patient continues to thrive at age 2 years.

Postmortem Examination (Twin A)

Heart

The autopsy was limited to the heart, which was enlarged. A large pulmonary trunk was situated to the right and pos-

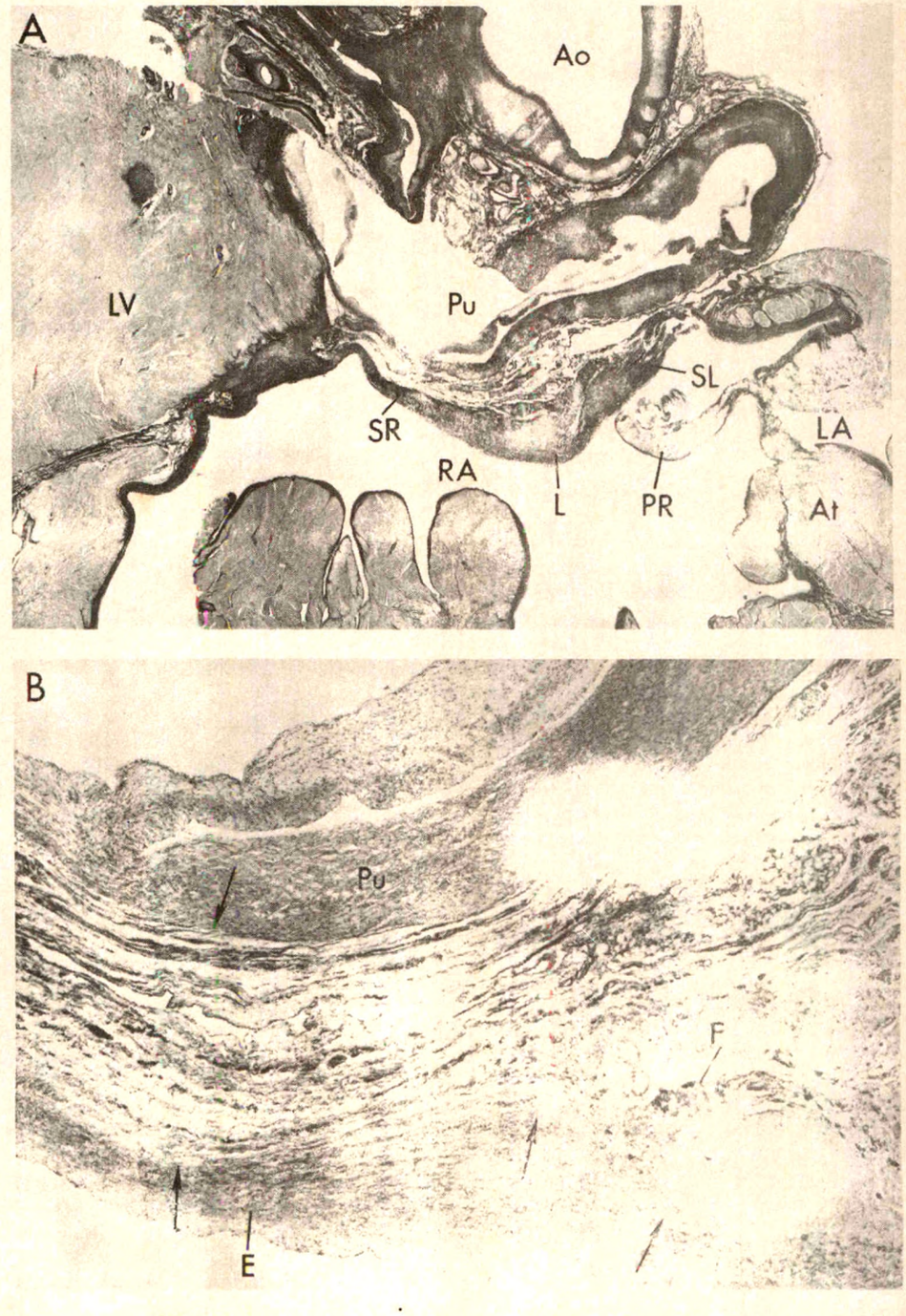

FIGURE 4. Photomicrographs of (**A**) superior (anterior) wall of both atria (Weigert-van Gieson stain × 17) and (**B**) superior wall of the right atrium (hematoxylin-eosin stain × 45). **Arrows** point to absent musculature. Ao = Aorta; At = posterior atrial septum; E = endocardial fibroelastosis; F = flecks of calcium; L = limbus fossae ovalis; LA = left atrium; LV = left ventricular musculature; Pr = derivative of septum primum; Pu = pulmonary trunk; RA = right atrium; SL = superior wall of left atrium; SR = superior wall of right atrium.

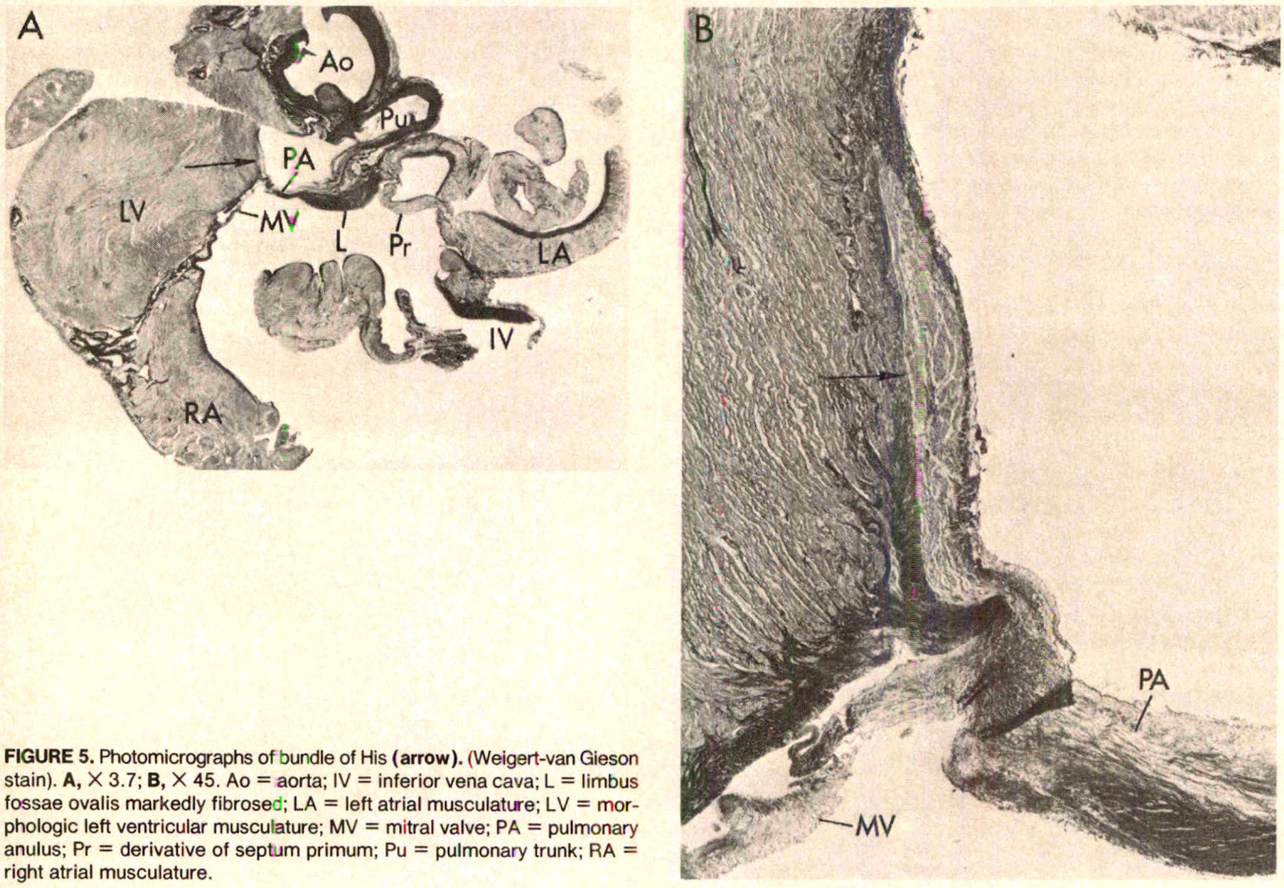

FIGURE 5. Photomicrographs of bundle of His **(arrow).** (Weigert-van Gieson stain). **A,** × 3.7; **B,** × 45. Ao = aorta; IV = inferior vena cava; L = limbus fossae ovalis markedly fibrosed; LA = left atrial musculature; LV = morphologic left ventricular musculature; MV = mitral valve; PA = pulmonary anulus; Pr = derivative of septum primum; Pu = pulmonary trunk; RA = right atrial musculature.

terior, and a smaller aorta to the left and anterior (Fig. 2). The normally placed morphologic right atrium emptied into the morphologic left ventricle, located to the right and anterior (Fig. 2 and 3). The normally placed morphologic left atrium emptied into the morphologic right ventricle, positioned to the left and posterior. The pulmonary trunk arose from the morphologic left ventricle (Fig. 2) and the aorta from the morphologic right ventricle. The left A-V (tricuspid) orifice was stenotic, and its valve consisted of a small leaflet on the inferior wall and another small leaflet adjacent to the ventricular septal defect. This defect was situated below the arch formed by the septal and parietal bands. Both A-V valves were contiguous at the ventricular defect and joined a curtain of endocardial tissue that lay beneath the pulmonary orifice (Fig. 2). The endocardium of the right atrium was diffusely thickened, especially around the limbic area and distal (downstream) to it, where ridge formation was evident. There was hypertrophy and enlargement of the right atrium and morphologic left ventricle. The left atrium was smaller than normal, but its wall was thicker than normal. The morphologic right ventricle was smaller and thinner than usual for a systemic ventricle. A patent ductus arteriosus and fetal coarctation were also present.

The fundamental anatomic diagnosis was mixed (discordant) levocardia with ventricular inversion (situs solitus atria with *l*-loop) with (1) common A-V canal type of ventricular septal defect, (2) fetal coarctation, and (3) tricuspid stenosis.

Conduction System Studies

Methods: The heart with the apex removed was completely embedded as a single block and serially sectioned roughly at right angles to the posterior wall but tilted somewhat toward the apex. Every fifth section was retained, and consecutive sections were stained with hematoxylin-eosin, Weigert-van Gieson and Gomori trichrome stains. In this manner 422 sections were studied.

Findings: *Sinoatrial (S-A) node.* This was in the normal position. A chronic organizing epicarditis was present with involvement of the periphery of the node. The epicarditis consisted of mononuclear cells, new vascular channels and perivascular fibrosis.

Approaches to S-A node. Chronic epicarditis was again seen.

Atria and atrial septum. The proximal part of the atrial septum and the atrial walls contained muscle. In the region of the fossa ovalis, the superior wall of the right atrium and to a lesser extent that of the left atrium adajcent to the pulmonary trunk were devoid of muscle (Fig. 4). In its place there was thick elastofibrous tissue with flecks of calcium, covered externally by abundant subepicardial loose fat and fibrous tissue with an infiltration of mononuclear cells. The endocardium in this region showed marked fibroelastosis. The limbus was partially replaced by marked fibrosis. The lesion also involved the distal (downstream) part of the anterior portion of the atrial septum.

Posterior A-V node and its approaches and posterior bundle. These were absent. Ordinary "working" atrial myocardium was present in the atrial septal region posteriorly.

Anterior A-V node and its approaches. These were absent. As stated, where one would expect these structures to be present (Fig. 3), there was no myocardium in the superior wall of the right atrium (Fig. 4).

Anterior bundle of His and bundle branches. The bundle commenced in the anulus of the mitral valve, slightly removed from the pulmonary valve anulus, and had no connections with the atrial musculature (Fig. 2 and 5). It passed into the superior wall of the morphologic left ventricle and continued laterally on the parietal wall of the left ventricle a short distance from the pulmonary anulus. It thus came to lie in the ventricular septum in the superodistal wall of the ventricular septal defect (Fig. 2 and 6). There it gave off fibers of the left bundle branch (Fig. 2) and then continued on the distal wall of the defect and gave off the right bundle branch (Fig. 2). The latter traveled through the septal wall to the right ventricular endocardium, branching into Purkinje fibers. The main bundle now was for a short distance intramyocardial. It then gave off the remaining fibers of the left bundle branch, which proceeded downward into the left ventricle. These fibers were not followed to their termination.

Mitral anulus. The atrial musculature of the lateral wall of the mitral anulus had a loose arrangement of small myocardial fibers resembling the cells seen in the approaches to the A-V node.

Atrial and ventricular myocardium. There was no evidence of fibrinoid necrosis or onion-skin perivascular fibrosis typical of disseminated lupus erythematosus. In some areas the atrial myocardium adjacent to the epicardium showed an infiltration of mononuclear cells.

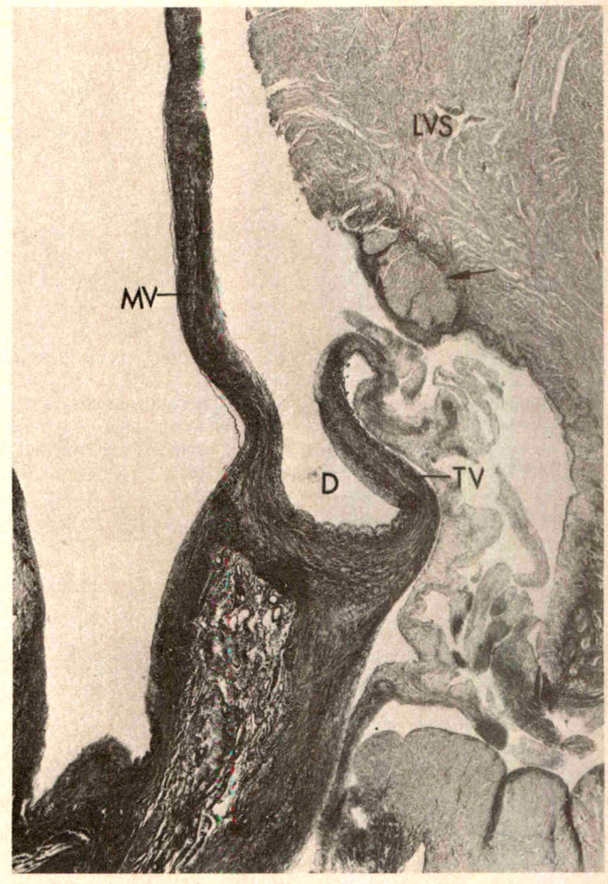

FIGURE 6. A-V bundle **(arrow)** in superodistal wall of ventricular septal defect. D = ventricular septal defect; LVS = morphologic left ventricular side of septal musculature; MV = mitral valve; TV = tricuspid valve.

Discussion

Congenital atrioventricular (A-V) block may be associated with various congenital malformations, or it may be found in an otherwise normal heart. It is especially common in mixed (discordant) levocardia with ventricular inversion (situs solitus atria with *l*-loop–corrected transposition).[1–13]

In pure levocardia (situs solitus atria with concordant chambers [*d* loop]), three mechanisms of block have been documented histologically (Fig. 7). They are (1) lack of connection between the atria and the peripheral conduction system,[18] (2) interruption of the bundle of His due to fibrosis,[19] and (3) interruption in the bundle branches.[20]

Block in an anterior type of conduction system in transposition: In most cases of mixed (discordant) levocardia with ventricular inversion (corrected transposition), an anterior type of conduction system has been described pathologically[14,15] and by His bundle studies[13,21–23] (Fig. 7). The posterior or normal A-V node may or may not be present (Fig. 3). When present, it usually does not give off a bundle of His and thus has no direct connection with the ventricles. In these cases, an A-V node is present anteriorly adjacent to the pulmonary and mitral anuli (Fig. 3 and 7). This node gives rise to a bundle of His, which penetrates the mitral anulus and travels along the superior parietal wall of the ventricle close to the pulmonary anulus. It thus reaches the left side of the ventricular septum (Fig. 2 and 7). If there is a ventricular septal defect, it reaches the superodistal wall of this defect, where the bundle branches are given off to their respective morphologic ventricular chambers.

When there is block in an anterior type of conduction system, fibrotic disruption of the bundle of His in the anterior bundle has been described in the two studies performed to date.[14,15] Our case is the first in which lack of connection of the atria with the peripheral conduction system was present in an anterior type of conduction system (Fig. 7). His bundle studies in corrected transposition have revealed block proximal or distal to the His bundle recording site.[11,24–26]

The lesion in "lack of connection," whether in an anterior or posterior type of conduction system, consists of lack of muscle in the approaches to the A-V node and intact or, as in our case, lack of muscle in the approaches and lack of an anterior A-V node, with the peripheral conduction system beginning in some part of the A-V bundle. Fibrosis, fat tissue with an infiltration of mononuclear cells and, in some cases, flecks of calcium take the place of the atrial muscle. No generalized myocarditis is present.

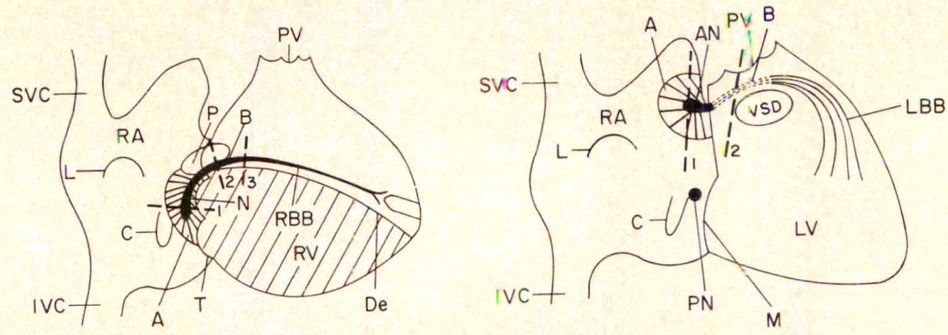

FIGURE 7. Diagrammatic sketches of the conduction system in pure levocardia **(left)** (atrioventricular [A-V] concordance [*d*-loop]) and in one type of mixed levocardia **(right)** (atrioventricular discordance [*l*-loop] as seen from the right side, and the sites of interruption that may be present. Note that the bundle of His in mixed levocardia is depicted by **dotted lines** to indicate that it is coursing on the parietal wall to reach the septum. **Dashed lines** labeled 1, 2 and 3 are areas in which interruption of the conduction system has been recorded in congenital A-V block: 1 = interruption in the A-V node and its approaches; 2 = interruption in the bundle of His; and 3 = interruption in the bundle branches. A = approaches to the A-V node; AN = anterior A-V node; B = bundle of His; C = opening of coronary sinus; De = demarcation between sinus and infundibulum of right ventricle; IVC = inferior vena cava; L = limbus fossae ovalis; LBB = left bundle branch; LV = left ventricle; M = mitral valve; N = normal (posterior) A-V node; P = pars membranacea; PN = posterior A-V node; PV = pulmonic valve; RA = right atrium; RBB = right bundle branch; RV = right ventricle; SVC = superior vena cava; T = tricuspid valve; VSD = ventricular septal defect.

Pathogenesis: The pathogenesis of this lesion, which is not yet known, is of special interest in our case. The mother of the infant had a positive rheumatoid factor on laboratory examination, although she had no symptoms of connective tissue dyscrasia and a normal antinuclear antibody pattern. This raises the question whether the pathologic findings in the atrial septum in our patient constitute a local myocarditis related to connective tissue dyscrasia, or whether the changes in the conduction system are in some other embryologic way related to the latter. In a recent study McCue et al.[17] reported a high incidence rate of congenital A-V block in children whose mothers have clinical or laboratory evidence of lupus erythematosus, implying that the possible passage of antibodies through the placenta may be responsible for the pathologic change in the conduction system.

Unfortunately we cannot answer this question. In previous cases in which lack of connection between the atria and the peripheral conduction system was found, no mention was made of tests for connective tissue dyscrasia in the mother. There was no evidence of lupus erythematosus in the atrial or ventricular myocardium in our patient or in any patient with congenital A-V block we have examined. This of course does not rule out possible antigen-antibody reaction manifesting itself in the peculiar lesion "lack of connection between the atria and the peripheral conduction system." The pathologic findings in the atrial myocardium and in the conduction system in our case may be the result of such a mechanism. In the future in all cases of congenital A-V block, the patient's mother should undergo laboratory tests for connective tissue dyscrasia. We believe that the epicarditis in our case was caused by the epicardial pacemaker and the intravenous pacemaker perforation of the ventricular myocardium.

If the changes in lack of connection between the atria and the peripheral conduction system are due to an embryologic variant, we previously suggested that an abnormality in the formation of the aortic fibrous prong of the central fibrous body during the absorption of the bulbus may be responsible for this lesion in a regular posteriorly oriented conducted system with no transposition.[18] We postulated that this prong may have involved the distal part of the atrial septum in an obliterative fibrotic process. This hypothesis may also explain the abnormal absorption of the bulbus in an anterior type of conduction system. In this type of system, the fibrous prong of the pulmonary portion of the bulbus adjacent to the mitral anulus may involve the superior walls of the adjacent atria, resulting in fibrosis and obliteration of the muscle of this area, which serves as the approach to the anterior A-V node. The calcification in this region, in some cases possibly dystrophic, supports this hypothesis.

Lateral to the lesion in the roof, the atrial muscle at the mitral anulus is suggestive of the cells of the approaches to the A-V node. This observation may support previous reports[27,28] that the atrial portion of the A-V rims has the potential to become conductive tissue. In our case both twins had A-V block. Familial congenital block and block in twins have previously been documented.[29–39]

References

1. **Walker WJ, Cooley DA, McNamara DG, et al:** Corrected transposition of the great vessels, atrioventricular block and ventricular septal defect. A clinical triad. Circulation 17:249–254, 1958
2. **Wright FS, Adams P Jr, Anderson RC:** Congenital atrioventricular dissociation due to complete or advanced atrioventricular heart block; clinical and cardiac catheterization findings in twelve children without cardiac malformations including three siblings. Am J Dis Child 98:72–79, 1959
3. **Nakamura FIK, Nadas AS:** Complete heart block in children. N Engl J Med 240:1261–1268, 1964
4. **Kango SJJ, Griffiths SP, Blumenthal S:** Congenital complete heart block: a classification and experience with 18 patients. Am J

Cardiol 20:632–638, 1967
5. **Berman DA, Adicoff A:** Corrected transposition of the great arteries causing complete heart block in an adult. Am J Cardiol 24:125–129, 1969
6. **Siggers DC, Deuchar DC:** Long-term use of implanted pacemakers in the control of complete heart block. Guys Hosp Rep 119: 323–328, 1970
7. **Jausseran JM, Amichot JL, Serafini V, et al:** Bloc auriculoventriculaire complet et transposition corigée des gros vaisseux. Marseille Med 107:305–312, 1970
8. **Hoffman JIE:** Heart block in congenital heart disease. Bull NY Acad Med 47:885–904, 1971
9. **Michaelsson M, Engle MA:** Congenital complete heart block: an international study of the natural history. In, Pediatric Cardiology (Engle MA, ed). Vol 4, no 3 in the series, Cardiovascular Clin (Brest AN, ed). Philadephia, FA Davis, 1972, p 85–101
10. **Rosell RC, Vidal FJA, Motilla VP, et al:** Transposicion corregida de los grandes vasos sin defectos associados. Presentacion de un caso con cono bilateralmente deficiente. Rev Esp Cardiol 26: 225–232, 1973
11. **Friedman HS, Lipski J, Pantazopoulos J, et al:** Bundle of His electrograms in congenital corrected tranposition of the great arteries. A study of two adult cases. Br Heart J 35:1307–1314, 1973
12. **Dupuis C, Bens JL, Brevière GM:** Les blocs auriculo-ventriculaires chez l'enfant. Schweiz Rundschau Med (Praxis) 64:787–795, 1975
13. **Fox LS, Kirklin JW, Pacifico AD, et al:** Intracardiac repair of cardiac malformations with atrioventricular discordance. Circulation 54: 123–127, 1976
14. **Lev M, Fielding RT, Zaeske D:** Mixed levocardia with ventricular inversion (corrected transposition) with complete atrioventricular block. A histopathologic study of the conduction system. Am J Cardiol 12:875–883, 1963
15. **Anderson RH, Becker AE, Arnold R, et al:** The conducting tissues in congenitally corrected transposition. Circulation 50:911–923, 1974
16. **Solomon MH, Winn KJ, White RD, et al:** Kartagener's syndrome with corrected transposition. Conducting system studies and coronary arterial occlusion complicating valvular replacement. Chest 69:677–680, 1976
17. **McCue CM, Mantakas ME, Tingelstad JB, et al:** Congenital heart block in newborns of mothers with connective tissue disease. Circulation 56:82–90, 1977
18. **Lev M, Silverman J, Fitzmaurice FM, et al:** Lack of connection between the atria and the more peripheral conduction system in congenital atrioventricular block. Am J Cardiol 27:481–490, 1971
19. **Lev M, Cuadros H, Paul MH:** Interruption of the atrioventricular bundle with congenital atrioventricular block. Circulation 43: 703–710, 1971
20. **Husson GS, Blackman MS, Rogers MC, et al:** Familial congenital bundle branch system disease. Am J Cardiol 32:365–369, 1973
21. **Stewart S, Manning J, Siegal L:** Automated identification of cardiac conduction tissue in L-TGV and Ebstein's anomaly. Ann Thorac Surg 23:215–220, 1977
22. **Maloney JD, Ritter DG, McGoon DC, et al:** Identification of the conduction system in corrected transposition and common ventricle at operation. Mayo Clin Proc 50:387–394, 1975
23. **Waldo AL, Maclean AH, James TN:** Electrtophysiologic delineation of the cardiac conduction system during open heart surgery. In, Cardiac Arrhythmias in the Neonate Infant and Child (Roberts NK, Gelband H, ed). New York, Appleton-Century-Crofts, 1977, p 373–403
24. **Rosen KM, Loeb HS, Gunnar RM, et al:** Mobitz type II block without bundle branch block. Circulation 44:1111–1119, 1971
25. **Gillette PCG, Reitman MJ, Mullin CE, et al:** Electrophysiology of ventricular inversion. Br Heart J 36:971–980, 1974
26. **Foster JR, Damato AN, Kline LE, et al:** Congenitally corrected transposition of the great vessels: localization of the site of complete atrioventricular block using His bundle electrograms. Am J Cardiol 38:383–387, 1976
27. **Anderson RH, Davies MJ, Becker AE:** Atrioventricular ring specialized tissue in the normal heart. Eur J Cardiol 2:219–230, 1974
28. **Wenink ACG:** Development of the human cardiac conduction system. J Anat 121:617–631, 1976
29. **Wendkos MH, Study RS:** Familial congenital complete A-V heart block. Am Heart J 34:138–142, 1947
30. **Khorsandian RS, Moghadam AN, Muller OF:** Familial congenital A-V dissociation. Am J Cardiol 14:118–124, 1964
31. **Crittenden IH, Latta H, Ticinovich DA:** Familial congenital heart block. Am J Dis Child 108:104–108, 1964
32. **Latta H, Crittenden IH:** Acquired lesions of the conduction system in familial congenital heart block. Lab Invest 13:214–221, 1964
33. **Rodriguez-Coronel A, Isenberg JI, Bliss HA:** Supernormal conductivity of the A-V node with anomalous A-V excitation in a patient with hereditary A-V block. Acta Cardiol 23:179–195, 1968
34. **McHenry MM, Cayler GG:** Congenital complete heart block in newborns, infants, children and recognition and treatment. J Natl Med Assoc 61:295–302, 1969
35. **Lynch HT, Mohiuddin S, Sketch MH, et al:** Hereditary progressive atrioventricular conduction defect. A new syndrome? JAMA 225:1465–1470, 1973
36. **James TN, McKone RC, Hudspeth AS:** Familial congenital heart block. Circulation 51:379–388, 1975
37. **James TN, Spencer MS, Kloepfer JC:** Adult onset syncope, with comments on the nature of congenital heart block and the morphogenesis of the human atrioventricular septal junction. Circulation 54:1001–1009, 1976
38. **Vallianos G, Sideris DA:** Familial conduction defects. Cardiology 59:190–197, 1974
39. **Schaall SF, Seidensticker J, Goodman R, et al:** Familial right bundle branch block, left axis deviation, complete heart block, and early death. A heritable disorder of cardiac conduction. Ann Intern Med 79:63–66, 1973

Coronary Bypass Surgery Weighed in the Balance*

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Coronary arterial surgery is under fire. In the recent preliminary report[1] of the Veterans Administration randomized prospective study of patients with chronic stable angina the survival rates did not differ between those who received medical treatment only and those who were surgically treated. In the 1972 to 1974 VA experience (excluding patients with lesions of the left main coronary artery), myocardial revascularization did not result in prolongation of life and medical treatment appeared to enhance longevity when compared with treatment prescribed in the 1960's. Armed with these data and fueled by Braunwald's editorial,[2] writers for the lay press reported that coronary arterial surgery has questionable lasting benefit and no effect on longevity; they then implied that this information is further proof that unnecessary surgery is practiced in the United States. Citing the VA report, the *New York Times*[3] noted that coronary bypass surgery would not be the first treatment to sweep the nation and later be found questionable. The editorial writer found a similarity between coronary bypass operations and an ineffective device used to freeze stomach ulcers. After a decade of progress in myocardial revascularization, are these conclusions justified?

A prospective randomized study of medical and surgical treatment requires adherence to a carefully designed protocol and evidence that the operation has been performed skillfully. The VA cooperative study does not meet these objectives. A survey of seven VA papers reporting on essentially the same patients[1,4–9] revealed poor definition of terms, inconsistent data, variability of experience and statistical error. Although randomization of patients in the VA study was partially based on the first arteriographic interpretation, these data were reclassified a year after termination of entry of patient to the study. This practice casts doubt on the quality or interpretation of the angiograms, and is inconsistent with the requirement of a randomized prospective study. In a 3 year follow-up period, 17 percent of those patients managed medically "crossed over" and were treated surgically. Presumably, the survival data on these crossover patients were altered as their therapy changed, but their fate was not stated. The total number of medical and surgical deaths and of patients lost to follow-up during each interval was not mentioned. Also, these reports failed to discuss the rehabilitative effects of surgical intervention, that is, effect on quality of life, ability to return to work, late symptoms and effort performance.

The results in this select population of patients with chronic stable angina pectoris led critics to suggest that modern medical treatment affords a substantially longer survival time in comparison with the natural course of coronary atherosclerosis documented from the 1960's.[10–14] However, the patient populations are not comparable. In selecting their population with chronic stable angina, the VA investigators excluded patients with (1) any form of unstable angina; (2) myocardial infarction in the preceding 6 months, or congestive failure in the 3 weeks before cardiac catheterization; (3) uncontrolled diabetes; (4) hypertension (under treatment) with a diastolic pressure of 100 mm Hg or greater; (5) ventricular aneurysm formation; (6) low ejection fraction; (7) marked elevation of left ventricular end-diastolic pressure; (8) left main coronary artery disease; or (9) diffuse nongraftable disease. Predictably, this low risk medical population will fare better than the cross section of patients with atherosclerotic heart disease whose natural history has been reported retrospectively.[10–14] In these latter studies, eligibility for coronary bypass operation was not considered.

The VA investigators wrote that "no standard medical therapeutic protocol" existed. Yet they gave credit to a "regularly supervised therapeutic program" for the low annual mortality rate of medically treated patients. The improved results of medical treatment have been attributed largely to the administration of propranolol to at least two thirds of the group. In 115 medically treated patients (37 percent) and 117 surgically treated patients (41 percent) in the VA study, the specific medical treatment was unknown. Therefore, only 39 percent of the medically managed patients were known

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to be taking propranolol versus 20 percent of the randomized surgically treated patients.

Of the 286 randomized surgically treated patients, 6 percent did not undergo surgery, 6 percent could not be categorized anatomically, 6 percent died at operation, 12 percent had all grafts closed on subsequent catheterization and 2 percent were lost to follow-up, leaving approximately 200 patients for assessment of surgical benefit. Excluding patients with obstruction of a single artery, who are known to have a high survival rate for at least 4 years, approximately 160 patients remain for comparison (about 60 percent of the original group). The high rate of incomplete revascularization (graft closure and incomplete attempt) and the 18 percent perioperative infarction rate[6] would obscure any benefit of surgical treatment.

Because of the rapid technological advances in recent years, any cardiac surgical experience that spans several years suffers from changing results. Today we see a lesser operative risk, reduced infarction rates and a higher rate of graft patency than we saw 5 years ago. Nevertheless, surgical results reported by the VA are substandard even for the years 1972 to 1974. Their randomization began with 21 participating hospitals; 10 dropped out, and 2 were added. Operative mortality rates ranged from 2 percent[15] to slightly more than 12 percent, a figure inconsistent with surgical mortality in that period. Such variations cannot be tolerated in a multicenter study. Braunwald[2] pointed out that an overall operative mortality rate of 5.6 percent was acceptable to him for that period and might also be an average mortality rate today for surgery performed outside major referral centers. Why should we judge a mode of therapy on the basis of mediocre performance? A high operative mortality rate, high perioperative infarction rate and low rate of graft patency are manifestations of technique. Demonstration of the utility of an operation to prolong life requires nearly ideal surgical results. The clinical trial is designed to study the operation, not the surgeon. Excellent operative results constitute a powerful stimulus to surgeons.

Among 1,400 consecutive surgical patients operated on at the Cleveland Clinic in 1973, which was the middle year in the VA study, the operative mortality rate was 0.6 percent. As in the VA reports, patients with severe left main arterial obstructions were excluded. A difference also exists between the VA perioperative infarction rate of 18 percent and the 4 percent infarction rate in our 1973 patients. Our graft patency rate in that period was 87 percent, which compares with the VA graft patency rate of 69 percent. With these data in mind, it is not surprising to find a 95 percent 3 year survival rate in our series in contrast to the VA surgical survival rate of 88 percent. Our experience is not unique.

If one applies the VA selection standards to our 1973 series,[16] 60 percent of our surgically treated patients would have been excluded by the VA standards. Among our patients who met the VA entrance criteria, the 3 year survival rate was 97 percent, adding further evidence that the VA series is indeed a low risk group that should experience a higher survival rate.

Braunwald's editorial,[2] entitled "Coronary Artery Surgery at the Crossroads," might better be retitled "Randomized Prospective Studies of Coronary Artery Disease at the Crossroads." No clinician argues with the potential validity of this investigative method. Clinical trials have enormous value. However, in the area of coronary bypass surgery, difficulty in conforming to the selection process, physician bias, nonuniformity of results in participating hospitals, failure of medical management causing a high crossover rate from medical to surgical treatment, and poor quality of surgery found in many participating hospitals introduce inaccuracies into the study, leading to erroneous conclusions that further confuse the physician. Critics of the operation discount anecdotal reporting of good surgical results for "lack of suitable controls."[17] In light of the rehabilitative effect of myocardial revascularization, it is unlikely and even impractical that proponents of bypass grafting will randomize large series to prove added longevity.

Granted, the cost of health care today is escalating. Hospital costs have soared from $10 billion in the 1950's to $130 billion in 1976, and coronary arterial surgery costs approximately $1 billion annually. However, priorities must be considered. Coronary atherosclerosis is the principal cause of death in the Western world and is responsible for death in half of the male population in the United States. As Rowe[18] observes, "Surgery is expensive, but how much is a left ventricle worth and to whom?" Medical treatment alone is not inexpensive. A patient receiving 160 mg of propranolol, 10 mg of isosorbide dinitrate four times daily and nitrobid will spend up to $500 yearly. This figure does not include costs of office visits, electrocardiograms, echocardiograms, stress testing or myocardial imaging. Of course, hospitalization and time lost from work affect overall costs. Hospitalization for angina pectoris or infarction may occur more frequently than is recognized. In the randomized prospective study of Mathur and Guinn,[19] 77 percent of the medically treated patients were hospitalized with a coronary event in the initial 5 year follow-up period.

No longer should medical and surgical treatment be viewed competitively. Coronary atherosclerosis requires lifelong medical management. Neither treatment cures the disease, but bypass surgery may complement conservative therapy and offer more effective rehabilitation. In many patients, especially those with severe angina, multivessel disease and technically favorable coronary anatomy, myocardial revascularization can improve life-style and extend longevity. When performed proficiently, the bypass operation provides relief from ischemic chest pain. For patients with multiple vessel disease,[20–25] angina with poor ventricular function,[26–28] unstable angina,[29–31] ventricular aneurysm[32,33] or left main coronary artery disease,[34,35] the effect of surgical treatment on longevity exceeds that of medical management. In fact, for elective revascularization alone, the 5 year actuarial survival rate is similar to survival curves for the normal population matched for age and sex.[36–40]

In the preliminary VA study, surgical treatment did not extend life in comparison with medical therapy. For

many other centers experienced in myocardial revascularization the record is entirely different. The recent criticism may be more aptly directed toward improving the quality of coronary bypass surgery found in randomized or nonrandomized studies. The track record of participating institutions should be thoroughly investigated in advance to avoid the embarrassment of wide discrepancies in results. Publication of mortality statistics and other pertinent information from each center will add credibility to a pooled study. Statistics and data retrieval can be as sophisticated as one wishes, but the surgical treatment under evaluation must be of high quality or comparisons are valueless.

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References

1. **Murphy ML, Hultgren HN, Detre K, et al:** Treatment of chronic stable angina. A preliminary report of survival data of the randomized Veterans Administration Cooperative Study. N Engl J Med 297:621–627, 1977
2. **Braunwald E:** Coronary-artery surgery at the crossroads. N Engl J Med 297:661–663, 1977
3. Editorial. How to bypass needless operations. *The New York Times*, January 3, 1978
4. **Hultgren HN, Takaro T, Detre K:** Medical versus surgical treatment of stable angina pectoris: progress report of a large scale study. Postgrad Med J 52:757–764, 1976
5. **Detre K, Hultgren H, Takaro T:** Veterans Administration Cooperative Study of surgery for coronary arterial occlusive disease. II. Methods and baseline characteristics, including experience with medical treatment. Am J Cardiol 40:212–225, 1977
6. **Read RC, Murphy ML, Hultgren HN, et al:** Survival of men treated for chronic stable angina pectoris: a cooperative randomized study. J Thorac Cardiovasc Surg 75:1–16, 1978
7. **Hultgren HN, Takaro T, Detre K:** Veterans Administration Cooperative Study of surgical treatment of stable angina. Preliminary results. Cardiovasc Clin 8:119–130, 1977
8. **Hultgren HN, Detre KM, Takaro T, et al:** The VA Cooperative Study of coronary arterial surgery. Baseline characteristics of study population and survival in subgroups with medical versus surgical treatment. Prog Cardiol 6:67–81, 1977
9. **Detre K, Murphy ML, Hultgren H:** Effect of coronary bypass surgery on longevity in high and low risk patients. Report from the VA cooperative coronary surgery study. Lancet 2:1243–1245, 1977
10. **Bruschke AVG, Proudfit WL, Sones FM Jr:** Progress study of 590 consecutive nonsurgical cases of coronary disease followed 5–9 years. I. Arteriographic correlations. Circulation 47:1147–1153, 1973
11. **Bruschke AVG, Proudfit WL, Sones FM Jr:** Progress study of 590 consecutive nonsurgical cases of coronary disease followed 5–9 years. II. Ventriculographic and other correlations. Circulation 47:1154–1163, 1973
12. **Oberman A, Jones WB, Riley CP, et al:** Natural history of coronary artery disease. Bull NY Acad Med 48:1109–1125, 1972
13. **Humphries JO, Kuller L, Ross RS, et al:** Natural history of ischemic heart disease in relation to arteriographic findings. A twelve year study of 224 patients. Circulation 49:489–497, 1974
14. **Proudfit WL, Bruschke AVG, Sones FM Jr:** Natural history of obstructive coronary artery disease. Ten-year study of 601 nonsurgical cases. Prog Cardiovasc Dis, in press
15. **Hultgren HN:** Controlled trials of coronary artery surgery. Presented at 50th Scientific Sessions, American Heart Association, Miami, FL, December 1, 1977
16. Cleveland Clinic Foundation, Cardiovascular Information Registry, established 1972. Unpublished data
17. **McIntosh HD, Garcia JA:** The first decade of aortocoronary bypass grafting, 1967–1977. Circulation 57:405–431, 1978
18. **Rowe GG:** Coronary-artery bypass surgery. Lancet 1:264, 1973
19. **Mathur VS, Guinn GA:** Sustained benefit from aorto-coronary bypass surgery demonstrated for 5 years. A prospective randomized study (abstr). Circulation 56:Suppl III:III-190, 1977
20. **Isom OW, Spencer FC, Glassman E, et al:** Does coronary bypass increase longevity? J Thorac Cardiovasc Surg 75:28–37, 1978
21. **Ullyot DJ, Wisneski J, Sullivan RW, et al:** Improved survival after coronary artery surgery in patients with extensive coronary artery disease. J Thorac Cardiovasc Surg 70:405–413, 1975
22. **Cohn LH, Boyden CM, Collins JJ Jr:** Improved long-term survival after aortocoronary bypass for advanced coronary artery disease. Am J Surg 129:380–385, 1975
23. **Sheldon WC, Rincon G, Pichard AD, et al:** Surgical treatment of coronary artery disease. Pure graft operations, with a study of 741 patients followed 3 to 7 years. Prog Cardiovasc Dis 18:237–253, 1975
24. **Hall RJ, Garcia E, Wukasch D, et al:** Long-term results of coronary artery bypass. Cardiovasc Dis Bull Texas Heart Inst 3:22–31, 1976
25. **Stiles QR, Lindesmith GG, Tucker BL, et al:** Long-term follow-up of patients with coronary artery bypass grafts. Circulation 54:Suppl III: III-32–III-34, 1976
26. **Isom OW, Spencer FC, Glassman E, et al:** Long-term survival following coronary bypass surgery in patients with significant impairment of left ventricular function. Circulation 52:Suppl I:I-141–I-147, 1975
27. **Manley JC, King JF, Zeft HJ, et al:** The "bad" left ventricle. Results of coronary surgery and effect on late survival. J Thorac Cardiovasc Surg 72:841–848, 1976
28. **Zubiate P, Kay JH, Mendez AM:** Myocardial revascularization for the patient with drastic impairment of function of the left ventricle. J Thorac Cardiovasc Surg 73:84–86, 1977
29. **Bertolasi CA, Trongé JE, Carreño CA, et al:** Unstable angina—prospective and randomized study of its evolution, with and without surgery. Am J Cardiol 33:201–208, 1974
30. **Matloff JM, Sustaita H, Chatterjee K, et al:** The rationale for surgery in preinfarction angina. J Thorac Cardiovasc Surg 69:73–81, 1975
31. **Manley JC, Zeft HJ, King JF:** Surgical treatment of unstable angina and the intermediate coronary syndrome (abstr). Circulation 56: Suppl III:III-61, 1977
32. **Loop FD, Effler DB, Navia JA, et al:** Aneurysms of the left ventricle. Survival and results of a ten-year surgical experience. Ann Surg 178:399–405, 1973
33. **Rogers WJ, Oberman A, Kouchoukos NT:** Left ventricular aneurysmectomy in patients with single versus multivessel coronary artery disease. Presented at 50th Scientific Sessions, American Heart Association, Miami, FL, December 1, 1977
34. **Oberman A, Harrell RR, Russell RO Jr, et al:** Surgical versus medical treatment in disease of the left main coronary artery. Lancet 2:591–594, 1976
35. **Takaro T, Hultgren HN, Lipton MJ, et al:** The VA cooperative randomized study of surgery for coronary arterial occlusive disease. II. Subgroup with significant left main lesions. Circulation 54:Suppl III:III-107–III-117, 1976
36. **Green GE, Kemp HG, Alam S, et al:** Coronary bypass surgery—five year follow-up of a consecutive series of 140 patients. Presented at 58th Annual Meeting, Am Assoc for Thorac Surg, New Orleans, May 8, 1978
37. **Loop FD, Irarrazaval MJ, Bredee JJ, et al:** Internal mammary artery graft for ischemic heart disease; effect of revascularization on clinical status and survival. Am J Cardiol 39:516–522, 1977
38. **Lawrie GM, Morris GC Jr, Howell JF, et al:** Special correspondence. N Engl J Med 297:1464, 1977
39. **Isom OW:** Discussion of Isom OW, Spencer FC, Glassman E, et al: Does coronary bypass increase longevity? J Thorac Cardiovasc Surg 75:37, 1978
40. **Kirklin JW:** Research related to surgical treatment in coronary artery disease. Presented at the 30th Anniversary of the American Heart Association and National Heart, Lung, and Blood Institute, Scientific Symposium. Current Horizons in Atherosclerosis and Hypertension, Washington, DC, Feb 9, 1978

Evaluation of the Efficacy of Coronary Bypass Surgery—I*

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For the participants in the
Veterans Administration Cooperative Study

Loop and his associates at the Cleveland Clinic[1] have chosen to interpret the recently published preliminary results of the Veterans Administration Cooperative Study as an attack on coronary surgery in the United States. Such an interpretation is incorrect. The published data refer primarily to survival.[2–6] The findings are clearly identified as preliminary; a definitive report will not be made until all surviving patients have been followed up for a minimum of 5 years. The reported survival data are essentially similar to data from three other controlled studies employing a similar protocol[7–9] and one large scale data bank study.[10] The results are also similar to those of two randomized studies of unstable angina[11–13] and one data bank study.[14] Reports from the Cooperative Study concerning relief of angina, changes in exercise performance and other aspects of the "quality of life" are currently being prepared for publication.

Areas of Agreement

The Cleveland Clinic group has made outstanding advances in the field of coronary surgery, and their publications attest to these contributions. On many points we are in complete agreement with Loop and his associates. These points may be summarized as follows:

1. *The VA Study was limited to male patients with stable angina, and there were many exclusions in the protocol.* The entry criteria and reasons for exclusion from the Study have been listed in reports from the VA Study.[3–5]

2. *The VA medical control group had a higher survival rate than that reported from other centers.* The Cleveland Clinic medical control group of 469 patients had a 4 year survival rate of 72 percent compared with the 83 percent survival rate in the VA Study. In patients with three vessel disease the Cleveland Clinic group reported a medical survival rate of 58 percent compared with a 76 percent survival rate in the VA Study.[15,16] Loop et al.[1] admit that the medical control group reported by the Cleveland Clinic is not a suitable group for a comparison of surgical results when they state, "In these latter studies eligibility for coronary surgery was not considered." A recent study[17] has shown that medical patients who are eligible for surgery have a substantially better survival rate than those who are not eligible. Unfortunately, results in surgically treated patients have been compared with results in inappropriate medical control patients in several studies, including one recently published by the Cleveland Clinic group.[16,18] These reports have promoted the unproved concept that surgery prolongs survival in most subgroups of patients with angina.

3. *Surgery has improved over the past 10 years, and coronary bypass surgery today can be performed with a very low mortality rate.* Data from the Cleveland Clinic and other centers support this view. Although part of the decrease in operative mortality is related to improvement in surgical methods, an important factor is improved patient selection, as Conley et al.[19] have pointed out.

4. *Surgery prolongs survival in symptomatic patients with left main coronary artery disease.*[2] We agree, although some workers do not.[20] Improved surgical survival has also been reported from nonrandomized studies in other subsets of patients, including those with three vessel disease with abnormal left ventricular function,[10] total occlusion of the right coronary artery and subtotal occlusion (more than 70 percent narrowing) of the left anterior descending coronary artery[21] or two vessel disease with severe left ventricular dysfunction.[22]

5. *Survival is excellent after coronary bypass surgery.* The survival rates of the surgically treated patients at the Cleveland Clinic are similar to the excellent survival rates of the surgically treated patients in the VA Cooperative Study.[4,5] For example, the Cleveland Clinic in 1975[15,16] reported on 741 patients who had coronary bypass surgery from 1967 to 1970. Surgical

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TABLE I

Comparison of 4 Year Survival Data in Surgically Treated Patients (Cleveland Clinic versus VA Study)

Survivors	Cleveland Clinic	VA Study
Total	88%	86%
With 1 vessel disease	92.8%	98%
With 2 vessel disease	89.4%	83%
With 3 vessel disease	86.4%	89%

skill was excellent in view of an operative mortality rate of 3.0 percent, a perioperative infarction incidence rate of 7.2 percent and graft patency in 84 percent of patients. Comparative 4 year survival data for the Cleveland Clinic patients and surgically treated patients in the VA Cooperative Study[5] are shown in Table I.

Areas of Disagreement

The five points listed represent substantial areas of agreement. What, then, are the areas of disagreement? It is evident that a major area of disagreement is failure of the VA Cooperative Study to show that surgery improved survival in any subgroup of patients except those with left main coronary artery disease.

Critics of the VA Study suggest that the failure to show improved survival in other subgroups is due to three factors: (1) The VA Study population had mild coronary disease and were not representative of patients being operated on in large private and academic surgical centers; (2) some patients randomized to medical therapy had surgery; (3) the surgery in the VA Study was inadequate. These points deserve comment:

Severity of coronary artery disease: Severe coronary disease is characterized by a low prevalence rate of single vessel disease and a high prevalence rate of three vessel disease, left main coronary artery disease, abnormal left ventricular function and electrocardiographic evidence of prior infarction. Clinical and angiographic features of patients operated on by the Cleveland Clinic group[15,16] and by the groups at Baylor,[23] at Duke[10,19] and in the VA Study[5] are shown in Table II.

These data do not indicate that patients in the VA Study had mild coronary disease. The characteristics of the surgically treated patients in the VA Study are very similar to those of the patients operated on at the Duke Medical Center during the same time period. The data also indicate that VA Study patients had more severe coronary disease than the patients reported on by the Cleveland Clinic and the Baylor groups. VA Study patients are therefore similar to patients operated on in large surgical centers in this country except for the presence of more severe coronary disease.

Crossover from medical to surgical treatment: Loop et al. and others have suggested that the presence of patients in the VA medical group who "crossed over" to surgical treatment may have resulted in better survival rates in the medical group and poorer survival rates in the surgical group. They suggest that if these patients had not been operated on, the medical group would have shown a lower survival rate. This is a valid criticism and should be examined.

The crossover patients did not exhibit more extensive disease or more adverse risk factors on entry than the other patients in the Study. Four year cumulative survival rates computed by four conceptually different methods of analysis give the results shown in Table III:

In Method 1, survival data of the medical group include data from the 41 patients who underwent surgery, and survival data of the surgical group include those of 18 patients whose operation was canceled. In Method 2, survival data of the medical group include those of all patients who did not have surgery (medical adherers and surgical nonadherers) and those of the surgical group include data from all those who had surgery (medical nonadherers and surgical adherers). In Method 3, survival data of the medical group include those of all medically randomized patients (the 41 medical nonadherers were followed up until the day before operation). Method 4 includes survival data for the 269 medical adherers and for the 267 surgical adherers. The lack of any significant difference in the results obtained with the four methods does not support the suggestion that the VA survival results are biased by the medical crossover patients.

Critics often assume that a crossover from medical to surgical treatment results primarily from increased severity of symptoms or development of unstable an-

TABLE II

Clinical and Angiographic Features of Patients Undergoing Bypass Surgery in VA Study and Three Major Centers

	Cleveland[15,16]	Baylor[23]	Duke[10,19]	VA[5]
Time period	1967–1970	1972–1973	1969–1976	1972–1974
Patients (no.)	741	1108	787	332*
Age (mean)	50	50	50	50
Coronary artery disease				
Single vessel	56%	18%	19%	14%
Three vessel	9.3%	38%	50%	52%
Left main	9.8%	7.5%	12%	14%
Abnormal LV function†	41%	28%	52%	78%
Prior infarction (ECG)	27%	39%	51%	41%
Operative mortality	3.0%	4.1%	5.4%	5.6%

* Of 332 assigned to surgery, 312 patients were operated on.

† Abnormal left ventricular function is not clearly defined in the reports from the Cleveland and Baylor groups. The definition of abnormal left ventricular function in the VA Study has been published.[3]

ECG = electrocardiogram; LV = left ventricular.

gina. This poses the question: Do severe symptoms indicate a poor prognosis? This question has been evaluated recently, and no relation was found between the severity of symptoms in patients with stable angina and the extent of coronary artery disease, left ventricular function or survival.[24] Does surgery improve survival in patients with unstable angina? Two randomized studies and one data bank study have not shown that survival is improved in unstable angina by surgical treatment.[11–14] Medical crossovers in the VA Study occurred for three reasons: (1) left main coronary disease, (2) increasingly severe symptoms with unstable angina in some of these patients, and (3) other factors not related to the presence of left main coronary disease or increasing symptoms. For these reasons we believe that the low medical crossover incidence rate in the VA Study has thus far not significantly affected the conclusions that can be derived from the Study.

Adequacy of surgical treatment: Was the surgery performed in the VA Cooperative Study inadequate? The operative mortality rate of 5 percent (vein bypass graft surgery only), the graft patency rate of 71 percent, with 89 percent of patients having at least one patent graft, and the number of grafts per patient (2.0) compares favorably with the surgical experience of many large surgical centers in the United States during 1972 to 1974. This was acknowledged in a paper from the Cleveland Clinic published in 1975[15] in which eight references were cited to support the statement that the operative mortality rate from other centers ranges from 3.4 to 7 percent. A more detailed comparison of the VA surgical experience with that of other surgical centers appears in the paper by Read et al.[5]

Another method of evaluating the adequacy of surgery is to examine the effect on symptoms and survival. In the VA Study 1 year after surgery 59 percent of patients had substantial relief or disappearance of angina and the condition of only 1 percent was worse. These results are comparable with those reported by many other workers.[7,10,25,26] The survival of the surgically treated patients in the VA Study (Table I) was similar to that of the patients treated surgically at the Cleveland Clinic.[15,16] If the VA surgery was inadequate one would expect to see a poorer survival rate in this group, especially considering that the VA patients had more severe coronary disease than the Cleveland Clinic patients. This was not the case. For these reasons, we believe that the surgery performed in the VA Cooperative Study is acceptable in regard to surgical standards of the 1972 to 1974 era and to the effect on symptoms and survival. Would improved surgical results have changed the VA survival data? This is an important question and deserves comment. Only a partial answer is possible. In 10 of the VA Study hospitals that contributed 80 percent of the patients to the Study, the operative mortality rate was 3.4 percent and the graft patency incidence rate 71 percent. Survival results from these 10 hospitals revealed no substantial difference from those of the total group.

Surgical results have improved since 1972 partly because of improved methods but probably also because of better patient selection.[19] Current surgical results in patients with coronary artery disease cannot be compared with the results of medical treatment employed from 1972 to 1974 because methods of medical treatment have also improved. There is now a greater use of propranolol, long-acting nitrates and antiarrhythmic drugs. There is increased emphasis on early hospitalization for symptoms of unstable angina, arrhythmias and left ventricular failure. There is a wider use of cardiopulmonary resuscitation by nonphysicians. Improvement has occurred in the treatment of serious arrhythmias, congestive failure and cardiogenic shock. In addition, there continues to be a decline in the death rate due to coronary artery disease in this country.[27] Thus, modern surgical methods must be compared only with modern medical methods of treatment of coronary artery disease.

TABLE III

Four Year Cumulative Survival Rates in VA Study Computed With Four Methods of Analysis

	Medical Group*		Surgical Group*	
	no.	% ± SE	no.	% ± SE
1. Original treatment allocation regardless of subsequent changes	310	84 ± 2	286	85 ± 2
2. Treatment received	287	84 ± 2	308	85 ± 2
3. Original treatment allocation with crossovers counted as lost at time of treatment change	310	86 ± 2	285	86 ± 2
4. Adherers to treatment	269	85 ± 2	267	86 ± 2

* Patients without left main coronary lesions randomized in 1972 to 1974. The analysis is based on data of October 1977.
SE = standard error.

Second reading of angiograms: The reference by Loop et al.[1] to the second reading of all angiograms in the Study makes an erroneous assumption. They misinterpreted the purpose and use of the second readings. Randomization was based solely on the initial angiographic interpretation. The second reading data were used for quality control and for additional data not obtained in the first reading.

Drugs: Loop et al. have estimated that only 39 percent of the medically managed patients were taking propranolol and they imply that this was not adequate medical treatment. The facts are as follows: In the medical treatment group 68 percent of patients were taking propranolol (mean dose 121 mg/day), 58 percent were using long-acting nitrates, 87 percent short-acting nitrates and 37 percent digitalis or diuretic agents.

Costs: Loop et al. are properly concerned about the impact of coronary surgery on the cost of medical care in the United States. It has been estimated that 325 coronary bypass operations were performed per million population in the United States in 1976.[28] This rate should be compared with the estimates per million for Australia (104), Scotland (92), England (20) and Sweden (19).[27,28] The advocacy of an expensive operation before its clinical effect has clearly been demonstrated can lead to a great waste of lives and valuable health care dollars.

For example, thousands of internal mammary ligations and internal mammary implantations were performed in the 1960's before controlled studies demonstrated that these operations did not decrease angina or prolong life.[29–31]

Effect on longevity: Loop et al. finally conclude that in five groups of patients with coronary disease "the effect of surgery upon longevity exceeds that of medical management." In one subgroup, that is, patients with left main coronary artery disease, we are in agreement on the basis of VA Cooperative Study data referred to by Loop et al.[2] In the other four subgroups no evidence of improved longevity was clearly demonstrated in eight appropriate controlled studies.[7–14] Statements that longevity is improved by coronary bypass surgery should not be made until clear scientific evidence is available from properly conducted studies. If coronary surgery is performed without regard to symptoms and solely to improve survival there will be a significant increase in the number of coronary arteriograms and operations performed annually in this country. The increased cost to the American public will be significant and may be intolerable.

It is possible that further follow-up and analysis of the VA Cooperative Study data will reveal additional subgroups of patients in whom survival is prolonged by surgery. In patients with three vessel disease and poor left ventricular function 4 year follow-up data suggest a possible favorable effect of surgery.[5] However, improvement in survival alone must be balanced against the complications and limitations of coronary arterial surgery that have been well presented in a recent review[27] and monograph.[32]

In 1980 when the final 5 year follow-up study of all patients in the 1972–74 VA Study cohort will have been completed and evaluated, a more complete answer to many of the questions raised by the Study should be available.

References

1. **Loop FD, Proudfit WL, Sheldon WC:** Coronary bypass surgery weighed in the balance. Am J Cardiol 42:154–156, 1978
2. **Takaro T, Hultgren HN, Lipton MJ, et al:** The VA Cooperative Randomized Study of Surgery for Coronary Arterial Occlusive Disease. II. Subgroup with significant left main lesions. Circulation 54: Suppl III:III-107–III-117, 1976
3. **Detre KM, Hultgren HN, Takaro T, et al:** Veterans Administration Cooperative Study of Surgery for Coronary Arterial Occlusive Disease. III. Methods and baseline characteristics, including experience with medical treatment. Am J Cardiol 40:212–225, 1977
4. **Murphy ML, Hultgren HN, Detre KM, et al:** Treatment of chronic stable angina—a preliminary report of survival data of the Randomized Veterans Administration Cooperative Study. N Engl J Med 297:621–627, 1977
5. **Read RC, Murphy ML, Hultgren HN, et al:** Survival of men treated for chronic stable angina pectoris: a cooperative randomized study. J Thorac Cardiovasc Surg 75:1–16, 1978
6. **Hultgren HN, Detre KM, Takaro T, et al:** Chapter on the VA Cooperative Study of Coronary Arterial Surgery: Baseline characteristics of study population and survival in subgroups with medical versus surgical treatment. In, Progress in Cardiology. VI. (Yu P, Goodwin J, ed). Philadelphia, Lea & Febiger, 1977, p 67–81
7. **Guinn GA, Mathur VS:** Surgery versus medical treatment for stable angina pectoris: prospective randomized study with 1- to 4-year follow-up. Ann Thorac Surg 22:524–527, 1976
8. **Kloster FE, Kremkau EL, Rahimtoola SH, et al:** Prospective randomized study of coronary bypass surgery for chronic stable angina. Cardiovasc Clin 8:145–156, 1977
9. **Aronow WS, Stemmer EA:** Two-year follow-up of angina pectoris: medical or surgical therapy. Ann Intern Med 82:208–212, 1975
10. **McNeer JF, Starmer CF, Bartel AF, et al:** Nature of treatment selection in coronary artery disease. Circulation 49:606–614, 1974
11. **Scheidt SS:** Unstable angina: medical management—or surgery? Cardiovasc Med 2:541–543, 1977
12. **Selden R, Neill WA, Ritzmann LW, et al:** Medical versus surgical therapy for acute coronary insufficiency: a randomized study. N Engl J Med 293:1329–1333, 1975
13. **Conti CR, Gilbert JB, Hodges M, et al:** Unstable angina pectoris: randomized study of surgical versus medical therapy (National Cooperative Unstable Angina Pectoris Study Group) (abstr). Am J Cardiol 35:129, 1975
14. **Hultgren HN, Pfeifer JF, Angell WW, et al:** Unstable angina: a comparison of medical and surgical management. Am J Cardiol 39:734–740, 1977
15. **Sheldon WC, Rincon G, Richard AD, et al:** Surgical treatment of coronary artery disease. Pure graft operations, with a study of 741 patients followed 3–7 years. Prog Cardiovasc Dis 18:237–253, 1975
16. **Hart N, Sheldon W:** Medical versus surgical management of myocardial ischemia. Practical Cardiol 4:74–90, 1978
17. **Gross H, Vaid A, Cohen M:** Prognosis in patients rejected for coronary revascularization surgery. Am J Med 64:9–20, 1978
18. **Ullyot DJ, Wisneski J, Sullivan RW, et al:** Improved survival after coronary artery surgery in patients with extensive coronary artery disease. J Thorac Cardiovasc Surg 70:405–413, 1975
19. **Conley MJ, Wechsler AS, Anderson RW, et al:** The relationship of patient selection to prognosis following aortocoronary bypass. Circulation 55:158–163, 1977
20. **DeMots H, Bonchek LI, Rösch J, et al:** Left main coronary artery disease. Risks of angiography, importance of coexisting disease of other coronary arteries and effects of revascularization. Am J Cardiol 36:136–141, 1975
21. **Mittler BS, Lee KL, Rosati RA:** Surgery vs. medical treatment in patients with totally-occluded right and subtotally-occluded left anterior descending coronary arteries (abstr). Circulation 51, 52:Suppl II:II-91, 1975
22. **Hammermeister KE, DeRouen TA, Murray JA, et al:** Effect of aortocoronary saphenous vein bypass grafting on death and sudden death: comparison of nonrandomized medically and surgically treated cohorts with comparable coronary disease and left ventricular function. Am J Cardiol 39:925–934, 1977
23. **Lawrie GM, Morris GC Jr, Howell JF, et al:** Improved survival beyond 5 years in 1108 patients undergoing coronary bypass (abstr). Am J Cardiol 41:355, 1978
24. **Peduzzi P, Takaro T, Murphy M:** Prognostic significance of symptoms in stable angina (abstr). Clin Res 26:484A, 1978
25. **Kouchoukos NT, Kirklin JW, Oberman A:** An appraisal of coronary bypass grafting. Circulation 50:11–16, 1974
26. **Tecklenberg PL, Alderman EL, Miller DC, et al:** Changes in survival and symptom relief in a longitudinal study of patients after bypass surgery. Circulation 51, 52:Suppl I:I-98–I-104, 1975
27. **McIntosh HD, Garcia JA:** The first decade of aortocoronary bypass grafting, 1967–1977: a review. Circulation 57:405–431, 1978
28. **Williams BT:** Coronary-artery bypass surgery. Lancet 1:264–265, 1978
29. **Cobb LA, Thomas GI, Dillard DH, et al:** An evaluation of internal-mammary-artery ligation by a double-blind technic. N Engl J Med 260:1115–1118, 1959
30. **Bhayana JH, Gage AA, Hultgren HN, et al:** VA Cooperative Study of Surgery for Coronary Arterial Disease. I. Internal mammary artery implantation (abstr). Circulation 51, 52:Suppl II:II-61, 1975
31. **Langston MF Jr, Kerth WJ, Selzer A, et al:** Evaluation of internal mammary artery implantation. Am J Cardiol 29:788–792, 1972
32. **Preston T:** Coronary Artery Surgery. A Critical Review. New York, Raven Press, 1977

Evaluation of the Efficacy of Coronary Bypass Surgery—II*

EUGENE BRAUNWALD, MD, FACC

Boston, Massachusetts

During the past decade coronary arterial bypass grafting has become one of the most common of all elective operations. The purpose of the randomized prospective Veterans Administration Cooperative Study, which has received so much attention, and of other similar prospective clinical trials is to determine the efficacy of this procedure in relation to survival. In this issue of the Journal, Loop and associates[1] criticize the preliminary report of the VA trial and its accompanying editorial, both published in the *New England Journal of Medicine*.[2,3] If objective, sober analysis of a method of treatment is interpreted as placing it "under fire," as asserted by Loop et al., then there is a real danger of a polarization of views that may inhibit rational discourse and clarification of the important issues involved.

In large measure, the remarks of Loop et al. attack a straw man. Neither the preliminary VA report nor my editorial states or implies that angina that is uncontrolled by vigorous medical therapy is *not* a strong indication for operation, nor does either suggest that the quality of life cannot be improved by the procedure. Even casual reading of my editorial will reveal three separate instances in a short (2 1/2 page) article emphasizing the effectiveness of the procedure in improving the quality of life by relieving anginal pain.

Quality of surgery and design of study: It is self-evident that the efficacy of surgery in prolonging life and relieving pain depends on the skill of the surgical team. A recent article by Read et al.[4] (unfortunately not quoted by Loop et al.) shows that the results of surgical treatment in the VA study are quite comparable with those of many other surgical groups. Indeed, a great deal of coronary bypass surgery performed in this country is inferior to that carried out by the VA. For example, Richter et al.[5] reported that in a group of community hospitals the average mortality rate after bypass surgery was 8.7 percent. Loop et al. did not cite these data or data from four other prospective randomized studies—two each in patients with stable and unstable angina—that do not indicate that coronary bypass surgery prolongs life, except in patients with disease of the left main coronary artery.[6–10] Some of these trials were carried out in this country's leading cardiac surgical centers.

Obviously, the validity and power of the conclusions of any study are only as great as the quality of the experimental design and the reliability of the data. The results of the VA trial are clearly not applicable to those institutions with results—in relation to mortality, perioperative infarction rate, graft patency and fraction of diseased vessels bypassed—that differ substantially from those in the VA study. I would expect, although it has not yet been convincingly demonstrated, that the long-term results of surgical treatment will be superior in institutions in which the quality of surgical treatment is distinctly better than it was in the VA study.

My editorial concluded that the preliminary results of the VA study are important and that the results of long-term follow-up of these patients and of those in other randomized trials of coronary bypass grafting will be awaited with intense interest. Surely, even the most casual student of medical history will acknowledge the frequency of noncritical, overenthusiastic acceptance of newly developed modes of therapy, whether medical or surgical. It has then taken many years, thousands of patients and enormous resources to place the particular drug or procedure into proper perspective. I believe that no greater disservice can be done to a new mode of treatment than to inhibit its critical, dispassionate evaluation *before* it becomes deeply rooted in everyday practice.

Need for randomized clinical trial: Some years ago, when the potential importance of coronary bypass surgery first became evident, I called for a randomized prospective clinical trial of the procedure.[11] Unfortunately, such a definitive trial has not yet been completed and, as a consequence, the most comprehensive study of the results of the operation to date, recently prepared by McIntosh and Garcia,[12] still reports many uncertainties. These authors concluded that "despite a low

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* Editorials published by the Journal reflect the views of the authors and do not necessarily represent the views of the Journal or of the American College of Cardiology.

operative mortality and rate of graft closure, available data in the literature do *not* indicate that initial symptomatic improvement necessarily persists, or that myocardial infarctions, arrhythmias, or congestive heart failure will be prevented, or that life will be prolonged in the vast majority of operated patients." The information presented by McIntosh and Garcia, taken as a whole, strengthens my conviction that it is unlikely that we will establish the efficacy of the bypass operation without the aid of proper randomized trials.

In commenting on the economic impact of the operation, Loop et al. neglected to mention the paper by Barnes et al.[12] from the University of Alabama, which showed no improvement in the number of hours that patients worked after coronary bypass grafting. Of course, the costs of medical therapy are substantial, and repeated hospitalizations add to the expense. However, there is no convincing evidence that surgical treatment reduces the number of hospitalizations for coronary artery disease. The question of the cost of treatment of an illness as life-threatening and as debilitating as coronary artery disease pales in importance next to the question of its efficacy. Insofar as the relief of angina is concerned, the operation is clearly effective in the majority of instances. The critical question is whether the operation prolongs life and this question has not yet been settled, save for patients with obstructive disease involving the left main coronary artery.

Neither dogmatic assertions nor screams of outrage will take the place of the firm data required to assess the efficacy of coronary bypass surgery. The VA Cooperative study, although certainly not perfect and not purporting to be the last word on the subject, is at least a step in the direction of rationally attempting to compare the results of two methods of management of chronic stable angina pectoris. One hopes that those who are so dissatisfied with the quality of this trial will carry out their own investigation of this critically important problem.

Need for both medical and surgical treatment: I agree with Loop et al. that the modern treatment of patients with coronary artery disease requires the intelligent application of both medical and surgical approaches. These should be used in a complementary, not competitive manner. Furthermore, the highest possible standards of care should be established and adherence to them should be insisted on for all patients, not merely those cared for in referral centers.

It is not in the best interests of our patients, the public or the medical profession to develop adversary positions between medical and surgical methods of treatment of coronary artery disease. Clearly, coronary bypass grafting is a major step forward in the treatment of coronary artery disease. However, far more information is needed before the operation can be accepted as the panacea it has been proclaimed to be by its more enthusiastic proponents. Although the many patients with this disease and their physicians must acknowledge their gratitude to the surgeons responsible for the development and perfection of coronary bypass grafting, our current lack of knowledge concerning the efficacy of the procedure, despite more than a decade's experience with more than 300,000 patients, is not one of which we should be proud. Our present dilemma may teach those who develop major new therapeutic techniques in the future to insist on their careful, objective assessment, by prospective randomized trials when necessary. These should be carried out after pilot studies have established the feasibility of the therapeutic maneuver but before the pressures become inescapable to apply it widely in clinical practice—that is, before the genie escapes from the bottle.[11]

References

1. **Loop FD, Proudfit WL, Sheldon WC:** Coronary bypass surgery weighed in the balance. Am J Cardiol 42:154–156, 1978
2. **Murphy ML, Hultgren HN, Detre K, et al:** Treatment of chronic stable angina. A preliminary report of survival data of the randomized Veterans Administration Cooperative Study. N Engl J Med 297:621–627, 1977
3. **Braunwald E:** Coronary-artery surgery at the crossroads. N Engl J Med 297:661–663, 1977
4. **Read RC, Murphy ML, Hultgren HN, et al:** Survival of men treated for chronic stable angina pectoris. A cooperative randomized study. J Thorac Cardiovasc Surg 75:1–16, 1978
5. **Richter MA, Dhurandhar R, O'Meallie LP, et al:** Aortocoronary bypass: early results of operations in community hospitals of greater New Orleans. South Med J 70:1052–1058, 1977
6. **Mathur VS, Guinn GA, Anastassiades LC, et al:** Surgical treatment of stable angina pectoris: prospective randomized study. N Engl J Med 292:709–713, 1975
7. **Guinn GA, Mathur VS:** Surgical versus medical treatment for stable angina pectoris: prospective randomized study with one to four year followup. Ann Thorac Surg 22:524–527, 1976
8. **Kloster FE, Kremkau EL, Rahimtoola SH, et al:** Prospective randomized study of coronary bypass surgery for chronic stable angina. Cardiovasc Clin 8:145–156, 1977
9. **Scheidt S:** Unstable angina: medical management—or surgery? Cardiovasc Med 2:541–543, 1977
10. **Selden R, Neill WA, Ritzmann LW, et al:** Medical versus surgical therapy for acute coronary insufficiency. N Engl J Med 293: 1329–1333, 1975
11. **Braunwald E:** Direct coronary revascularization. A plea not to let the genie escape from the bottle. Hosp Practice 6:9–10, 1971
12. **McIntosh HD, Garcia JA:** The first decade of aortocoronary bypass grafting, 1967–1977. A review. Circulation 57:405–431, 1978
13. **Barnes GK, Ray MJ, Oberman A, et al:** Changes in working status of patients following coronary bypass surgery. JAMA 238: 1259–1262, 1977

CALENDAR OF EXTRAMURAL PROGRAMS

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Extramural Programs Department, Division of Continuing Education, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

JULY 1978 THROUGH OCTOBER 1978

To be arranged individually Preceptorships in Cardiology. Arthur Selzer, FACC, director, Pacific Medical Center, San Francisco, CA

AUG. 26–28 **Tutorials in the Tetons: Cardiac Emergencies (Fourth Annual).** Robert S. Eliot, FACC, director and Alan D. Forker, FACC, William P. Nelson, FACC and Gerald L. Wolf, co-directors. Jackson Lake Lodge, Moran, WY

SEPT. 7–9 **The Clinical Pharmacology of Cardiovascular Drugs.** William B. Abrams, FACC, Albert N. Brest, FACC, Richard O. Davies, FACC and Roger F. Ferguson, co-directors. Marriott Motor Hotel, Philadelphia, PA

SEPT. 11–14 **Electrocardiography: Core Curriculum and Self-Assessment.** Paul L. McHenry, FACC, director and Charles Fisch, FACC, co-director. Myers Auditorium, Wishard Memorial Hospital, Indiana University Medical Center, Indianapolis, IN

SEPT. 11–14 **Electrocardiography: Core Curriculum and Self-Assessment.** Arthur Selzer, FACC, director. Golden Gateway Holiday Inn, San Francisco, CA

SEPT. 27–29 **Advanced Echocardiography.** Harvey Feigenbaum, FACC, director and Betty C. Corya, James C. Dillon, FACC and Arthur E. Weyman, FACC, co-directors. Indianapolis Hilton Hotel, Indianapolis, IN

OCT. 12–14 **Cardiology Update—1978.** William W. Parmley, FACC and Kanu Chatterjee, FACC, directors. Del Monte Hyatt House, Monterey, CA

OCT. 13–14 **Geriatric Cardiology. Physiologic vs. Pathologic Aging of the Cardiovascular System: Clinical Applications and Therapeutic Considerations.** Borys Surawicz, FACC and Raymond Harris, FACC, directors. Hyatt Regency Lexington, Lexington, KY

OCT. 18–20 **Cardiac Pacing.** Doris J. W. Escher, FACC and Seymour Furman, FACC, directors. Waldorf-Astoria Hotel, New York, NY

OCT. 19–21 **Valvular Disease—Practical Diagnosis and Management.** Peter C. Gazes, FACC, director and Charles P. Summerall III, FACC, Grady H. Hendrix, FACC, William H. Barnwell II, FACC, Bruce W. Usher, FACC, J. Lindsay Leviner, Jr. and Robert G. Irvin, co-directors. Kiawah Island Inn, Kiawah Island, Charleston, SC

LEARNING CENTER: PROGRAM CALENDAR

The American College of Cardiology's newest department, the Learning Center, located at the College's Bethesda, Maryland headquarters, began operations last October with the offering of its first continuing medical education program for physicians with a specialty or an interest in cardiovascular medicine. The purpose of the Learning Center is to support the professional commitment to quality patient care by providing a new standard of excellence in cardiovascular continuing education. For additional information concerning the programs listed below or for a complete schedule of programs through December 1978, contact Program Coordinator, Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014 (301) 897-5400.

AUGUST THROUGH DECEMBER 1978

Month/Dates	Course Director	Title of Program
August 7–10	R. Joe Noble, MD, FACC	**Update in Cardiology**
September 25–27	Kenneth M. Rosen, MD, FACC	**Evaluation of Arrhythmias with His Bundle Recording and Cardiac Stimulation**
October 4–6	Charles E. Rackley, MD, FACC	**Clinical Evaluation and Treatment of Coronary Artery Disease**
October 19–21	Pravin M. Shah, MD, FACC	**Adult Echocardiography: Clinical Applications–M-Mode vs 2-Dimensional**
October 23–25	Douglas P. Zipes, MD, FACC	**The Ubiquitous PVC: Sorting Out the Dilemma**
November 6–8	Ralph Shabetai, MD, FACC	**Management of Pericardial and Myocardial Disease**
December 4–6	Borys Surawicz, MD, FACC	**Interpretation of ECGs**
December 11–13	Victor Parsonnet, MD, FACC	**Current Concepts in Pacing: An Individualized Seminar Approach**

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28. Schiebler GL, Van Mierop LHS, Krovetz LJ: Diseases of the tricuspid valve, chap 20. In, Heart Disease in Infants, Children and Adolescents (Moss AJ, Adams F, ed). Baltimore, Williams & Wilkins, 1968, p 134

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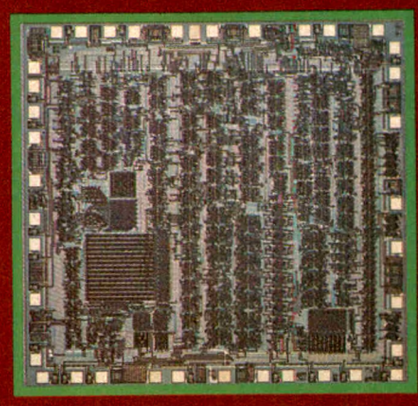

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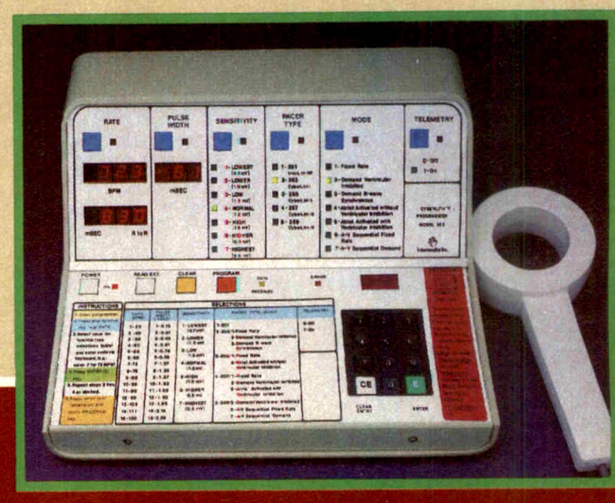

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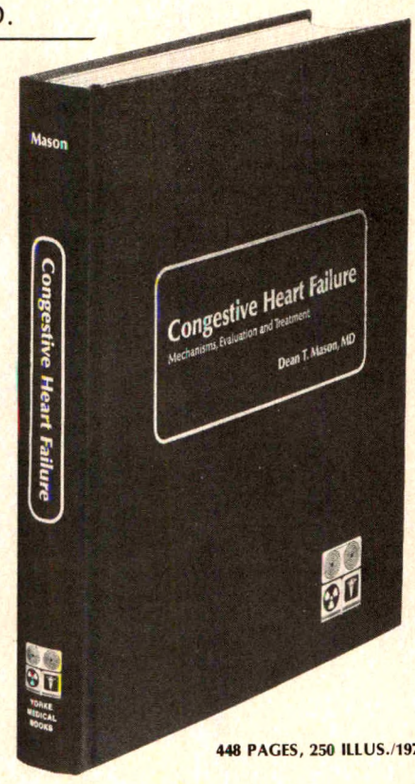

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About the author . . . Dean T. Mason, M.D.

Professor of Medicine, Professor Physiology, Chief of Cardiovascular Medicine, University of California, School of Medicine, Davis

President, American College of Cardiology President, Western Society for Clinical Research

Member of the American Board of Internal Medicine Cardiovascular Diseases

Has authored more than 400 original articles on cardiovascular science and clinical cardiology.

Serves on the editorial boards of The American Journal of Cardiology, The Journal of Clinical Investigation, Circulation, Chest, Clinical Pharmacology and Therapeutics, Catheterization and Cardiovascular Diagnosis, and Heart and Lung.

Recipient of Experimental Therapeutics Award in 1973 from the American Society of Pharmacology and Experimental Therapeutics, the Research Awards in 1965 from the American Therapeutic Society, and the Theodore and Susan B. Cummings Humanitarian Awards in 1972, 1973, and 1975 from the U.S. State Department and the American College of Cardiology.

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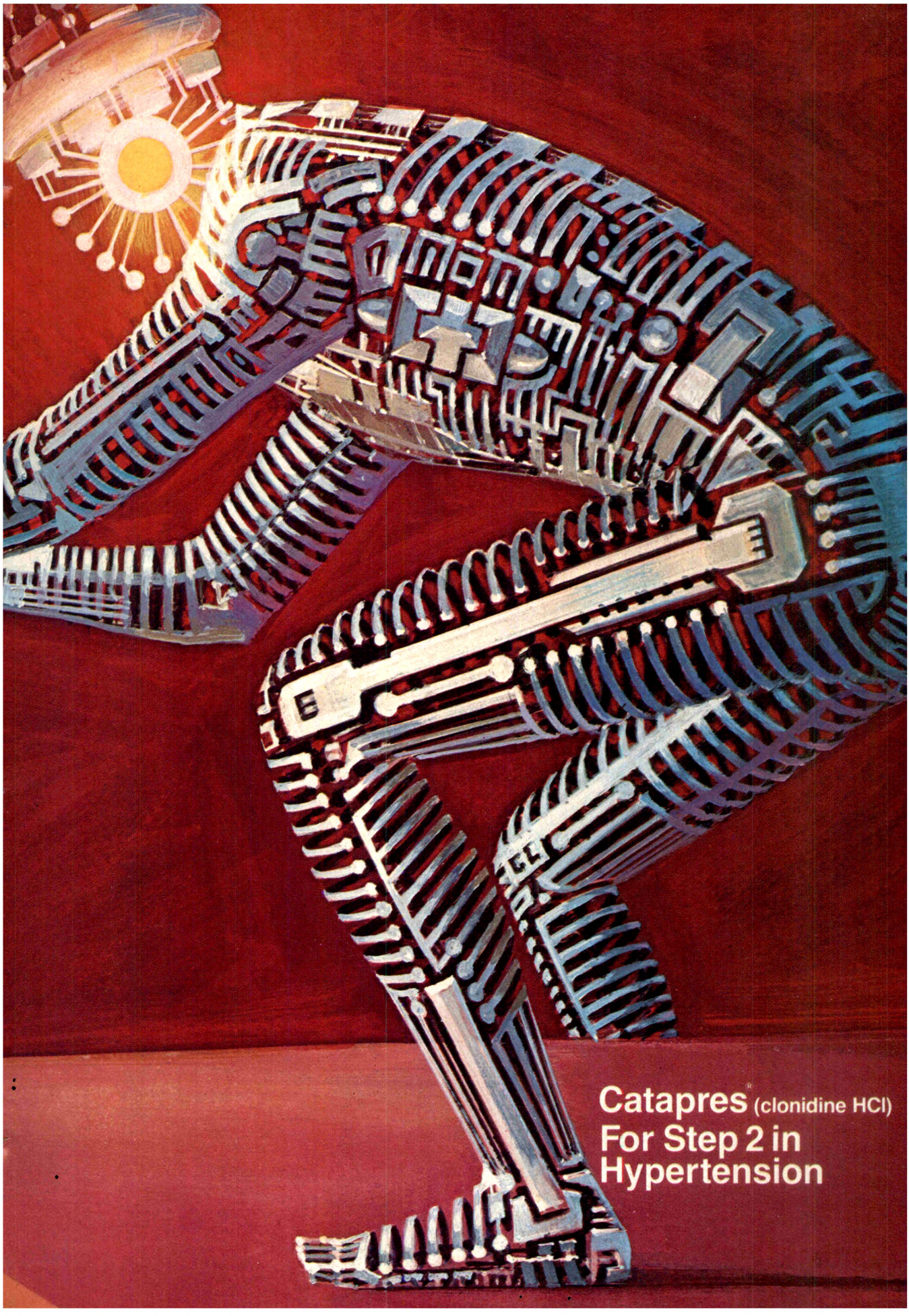
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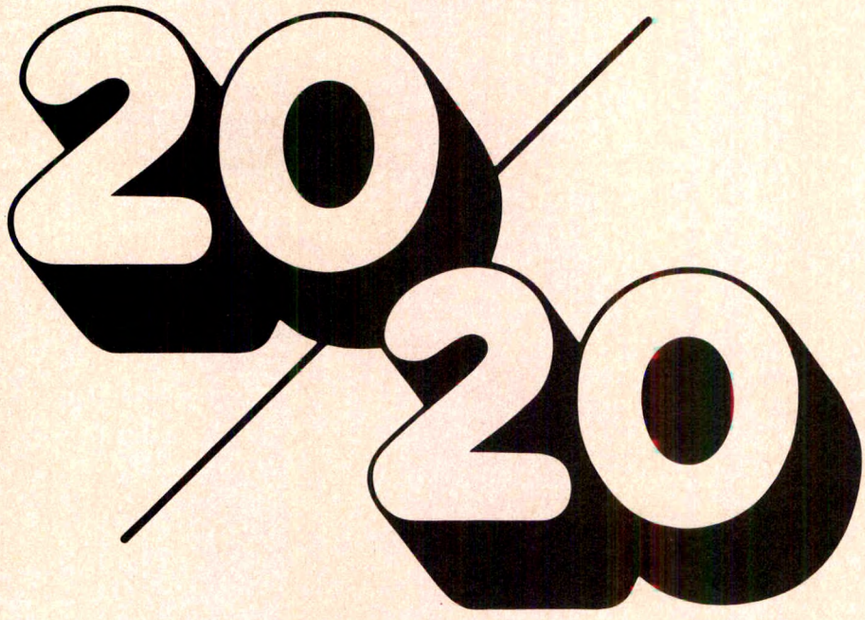

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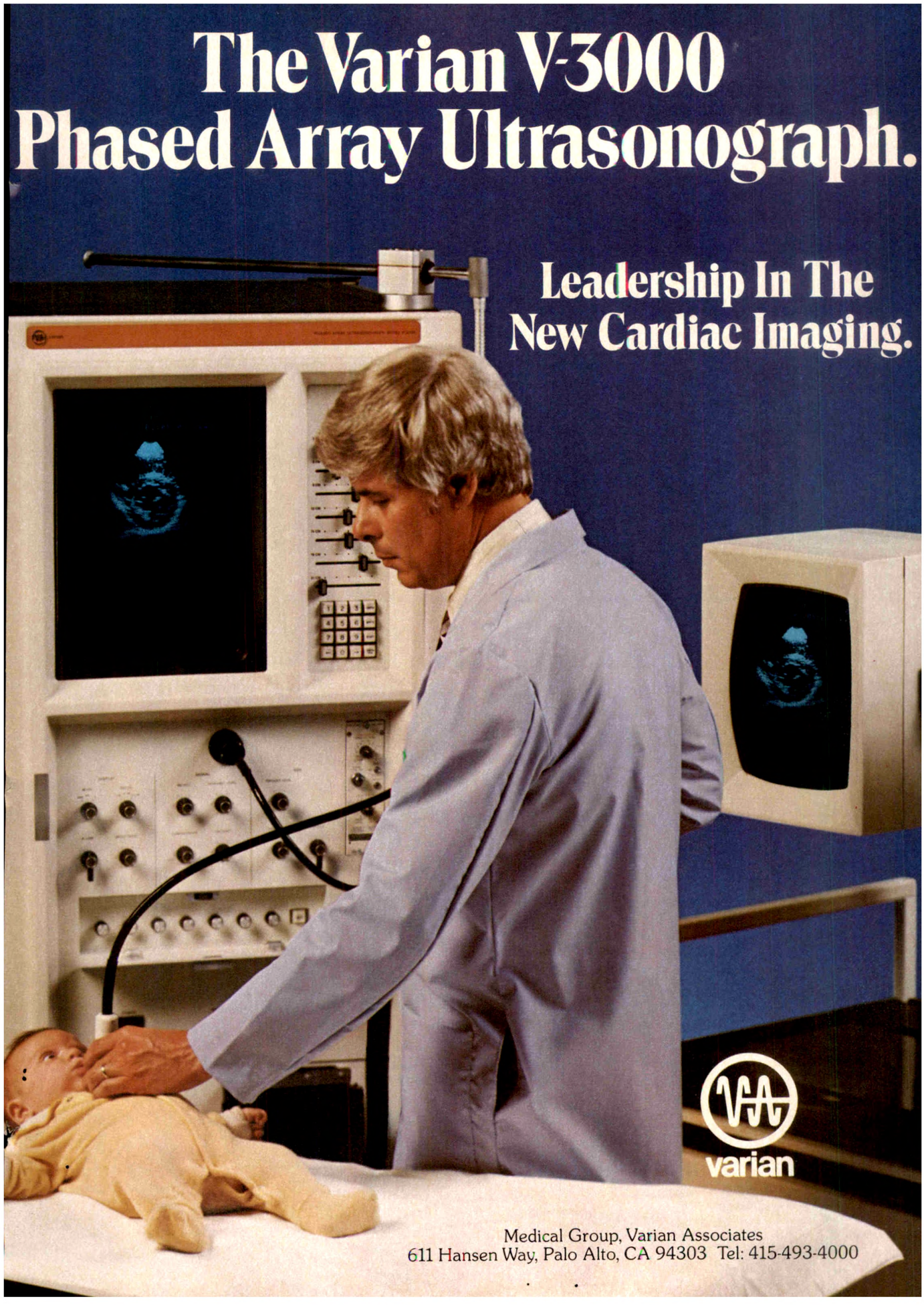

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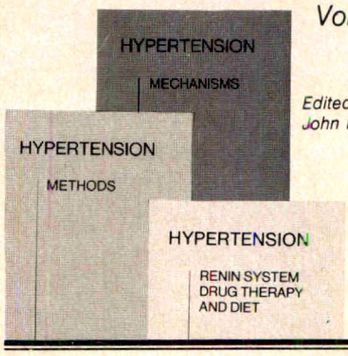

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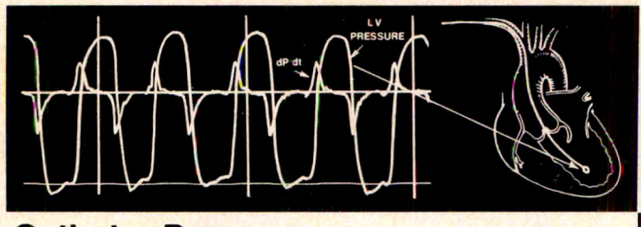

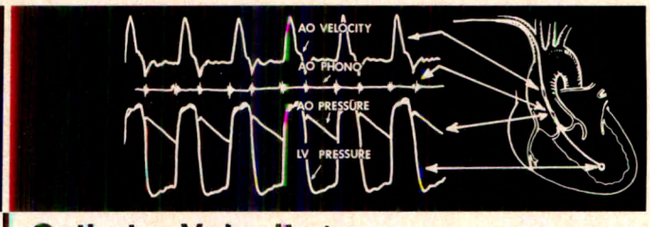

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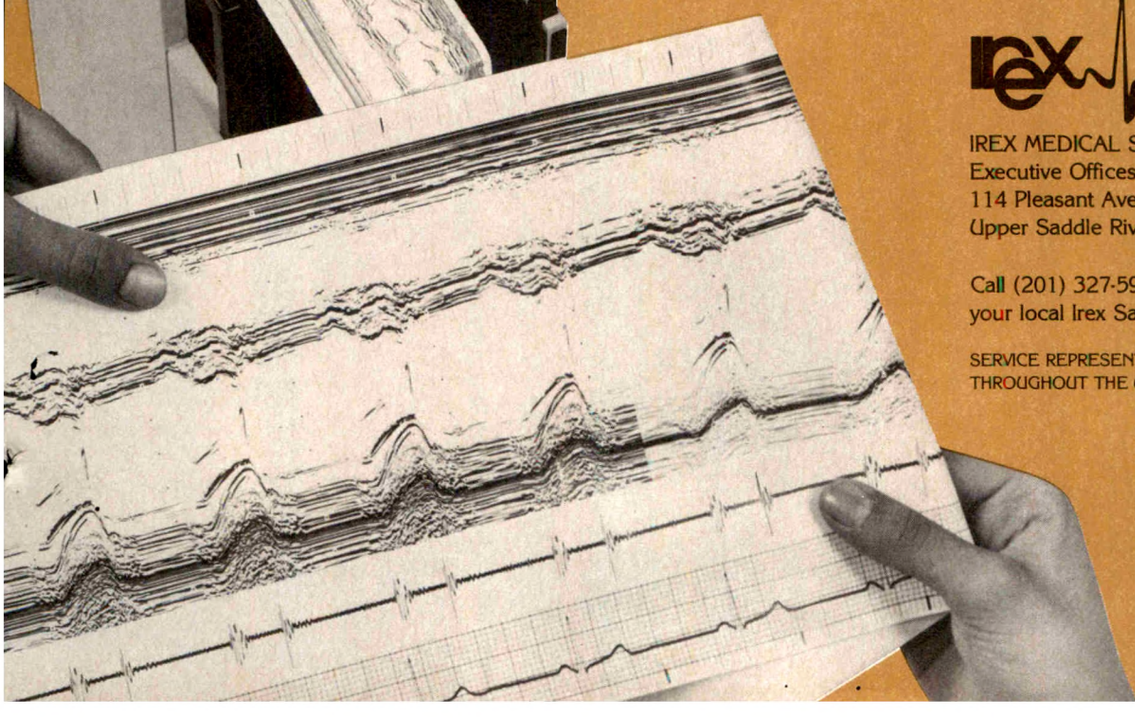

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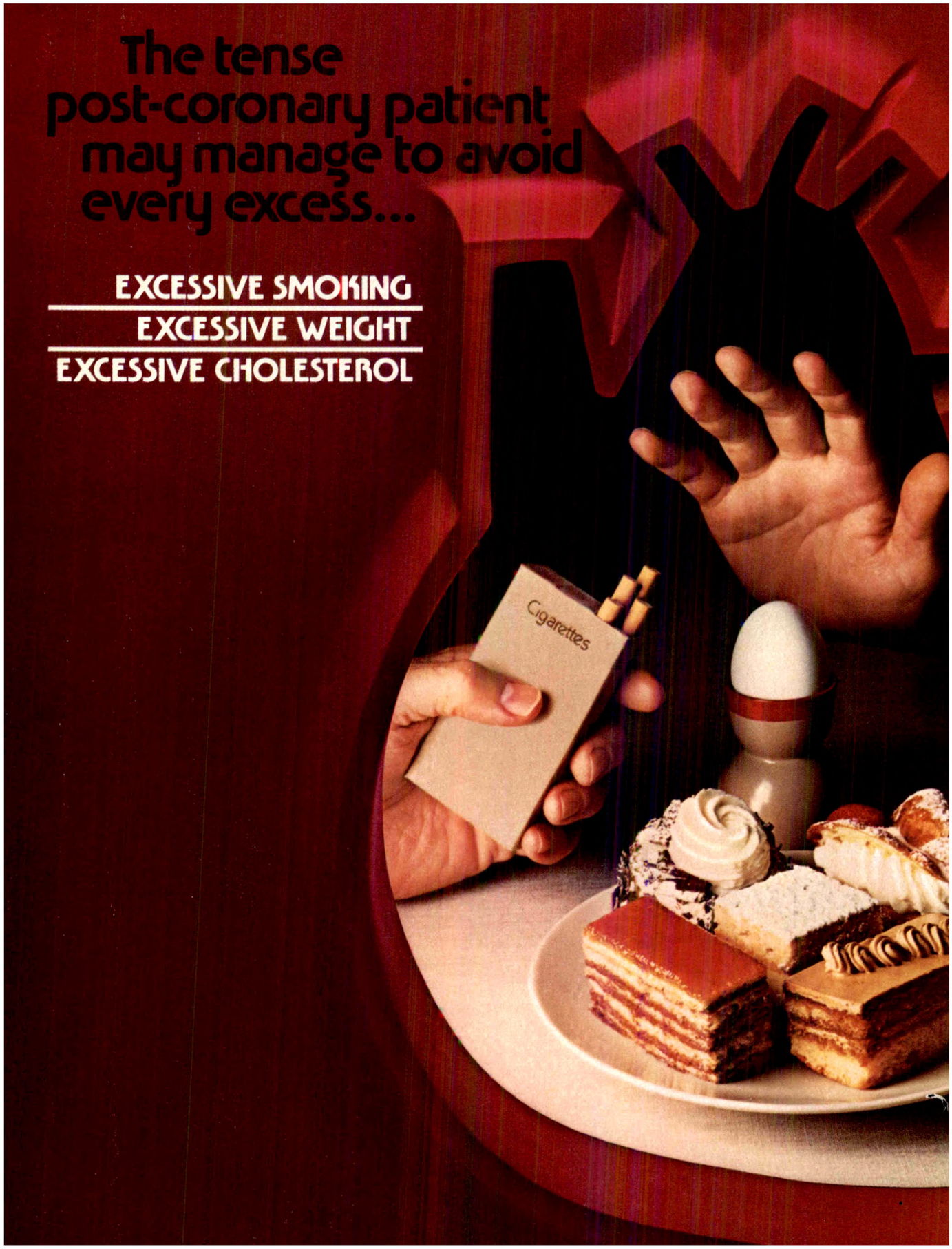
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The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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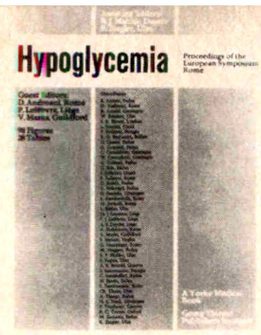

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This European (Rome) Symposium was the first free interchange of ideas among scientists in the various medical disciplines—physiology, internal medicine, endocrinology, clinical biochemistry, etc.—necessary to the understanding, diagnosis and treatment of hypoglycemia. The concentration was on the various aspects of insulin-producing tumors and the vexed question of essential reactive hypoglycemia. Special attention was given to the widespread misinterpretation of laboratory data relating to the prolonged oral glucose test which has resulted in the erroneous belief that "millions suffer from hypoglycemia."

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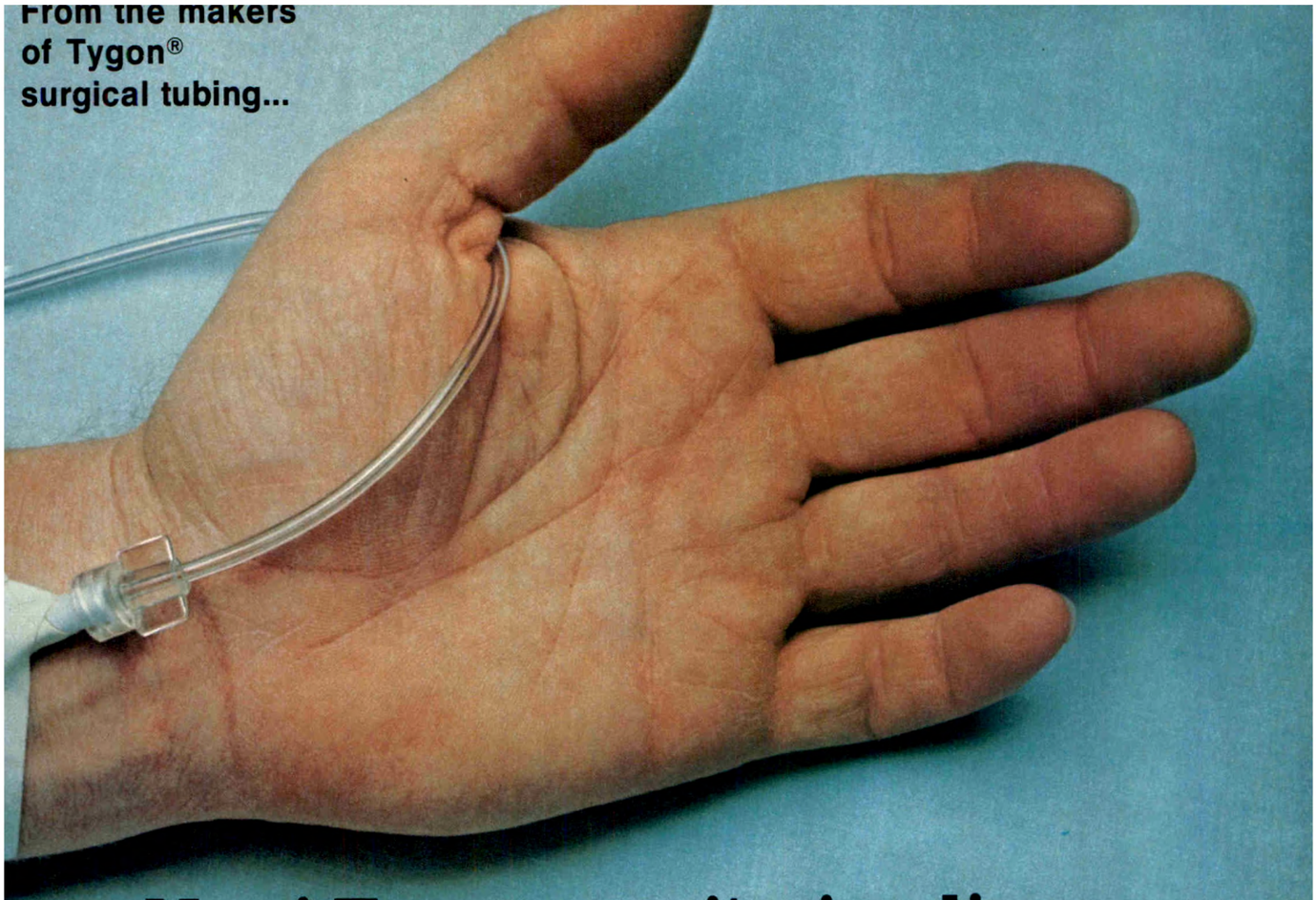

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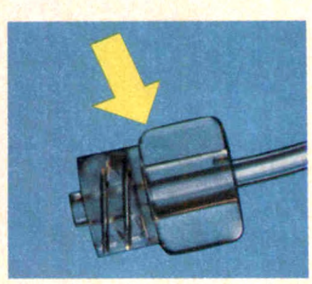

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New wide-angle probe for EkoSector I.™

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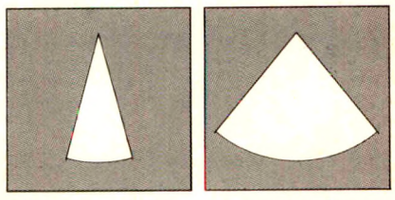
Our remarkable new wide-angle probe gives you an enlarged cross-sectional scan of the heart, making it easier for you to visualize and correlate relative position and motion patterns of intracardiac structures for a more accurate diagnosis.

In addition this new probe provides an image of extremely high resolution.

More innovation without obsolescence.

The new wide-angle probe is yet another SKI innovation designed to protect your original investment while providing extra value to you.

If you already own an EkoSector I™, a modification will enable you to use the standard probe and the new wide-angle probe interchangeably. Both heads simply attach to the existing probe handle.



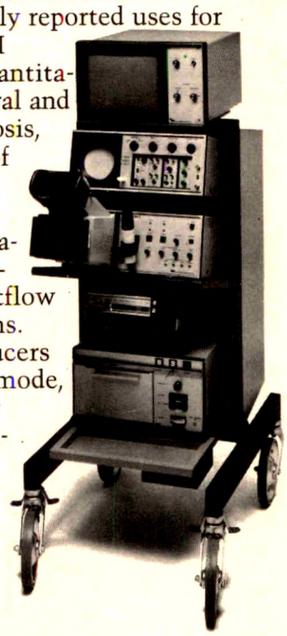
The new wide-angle probe displays a scan that is 50° greater than the standard 30° probe. Both probes will be supplied with all new EkoSector I units. The wide-angle probe is supplied for existing systems as an optional accessory.

Real-time cross-sectional scanning and unique design.

The SKI patented direct processing method provides distortion-free electronic images and correct, spatially-oriented, information concerning the depth relative to the chest wall, and real-time motion of cardiac structures.

Clinically reported uses for EkoSector I include quantitation of mitral and aortic stenosis, detection of ventricular aneurysms and localization of ventricular outflow obstructions.

Transducers provide A-mode, M-mode or sector scanning of the heart or other organs. Images can be displayed on the oscilloscope or on the large external X-Y monitor. A videotape recorder allows recording of M-mode or cross-sectional scans along with verbal comments. Playback can be at normal speed, slow motion or stop-frame projection. Recorded images can be selectively altered in size by means of the tissue depth control.



If you already own an Ekoline 20A, the EkoSector I can easily be interfaced with it, cutting your cost for the whole system by almost half. Even if you do not already own an Ekoline 20A, the complete system still costs less than competing systems.

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For ventricular arrhythmias.
For atrial arrhythmias.
For smooth, trouble-free conversion.
For steady maintenance.

CARDIOQUIN®
TABLETS
(quinidine polygalacturonate)

- ☐ Greater GI tolerance than with quinidine sulfate
- ☐ Full quinidine cardiodynamics
- ☐ Convenient b.i.d. or t.i.d. dosage for most patients

CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm—whether with CARDIOQUIN Tablets or electroconversion—only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases. The polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 50.

Purdue Frederick

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AUGUST 1978

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The American Journal of CARDIOLOGY®

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Miami Beach, Florida, March 11–15, 1979

Contents on Page A6

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logical therapy for the vast
who need more or other

Logical therapy because essential hypertension is usually characterized by elevated peripheral resistance with normal cardiac output. ALDOMET lowers blood pressure apparently by lowering peripheral resistance—while cardiac output is usually maintained.

Appropriate for all degrees of hypertension when drug therapy is required

Highly effective in mild, moderate, or severe hypertension, ALDOMET (Methyldopa, MSD) is useful when there has been an inadequate response to initial thiazide therapy, or as initial therapy when thiazides are deemed inappropriate or contraindicated (for example, when hypersensitivity to sulfonamide-derived drugs exists).

Appropriate for many hypertensive patients requiring special consideration

- hypertensive patients with renal impairment—ALDOMET usually does not reduce glomerular filtration rate, renal blood flow, or filtration fraction. (Methyldopa is largely excreted by the kidney, and patients with impaired renal function may respond to smaller doses.)
- hypertensive children requiring drug therapy (See pediatric dosage recommendations in the addendum on the last page of this advertisement.)

Not contraindicated in the following coexisting conditions in which some other antihypertensives are contraindicated

- congestive heart failure (Edema may occur with ALDOMET. This is usually relieved by the use of a diuretic, but if edema progresses methyldopa should be discontinued.)
- coronary artery disease (Aggravation of angina pectoris may occur with ALDOMET.)
- mitral valvular rheumatic heart disease
- bronchial asthma
- allergic rhinitis during the pollen season
- greater than first-degree heart block
- active peptic ulcer
- ulcerative colitis

majority of hypertensives
therapy than a thiazide...

Therapeutic limitations

ALDOMET is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previous methyldopa therapy has been associated with liver disorders.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, please see the brief summary of prescribing information.

TABLETS: 500 mg, 250 mg, and 125 mg

ALDOMET®
(METHYLDOPA | MSD)

MSD
MERCK SHARP & DOHME

For a brief summary of prescribing information, please see following page.

TABLETS: 500 mg, 250 mg, and 125 mg

ALDOMET®
(METHYLDOPA | MSD)

Logical therapy for the vast majority of hypertensives who need more or other therapy than a thiazide

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor.

Allergic: Drug-related fever, lupus-like syndrome, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 500.

For more detailed information, consult your MSD representative or see full prescribing information.

Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

J8AM17(709)

addendum

MSD MERCK SHARP & DOHME

DOSAGE INFORMATION ON ALDOMET® (Methyldopa | MSD)

Adults

initiating therapy

- 250 mg b.i.d. or t.i.d. the first 48 hours
- increase or decrease, preferably at intervals of not less than two days, until response is adequate
- start dosage increases in the evening to minimize sedation
- adjusting dosage may prevent morning hypotension without losing control of afternoon blood pressure
- when ALDOMET is added, the dosage of thiazides need not be changed
- when given with antihypertensives other than thiazides, the dose of these agents may have to be adjusted and the starting dosage of ALDOMET should be limited to 500 mg daily in divided doses

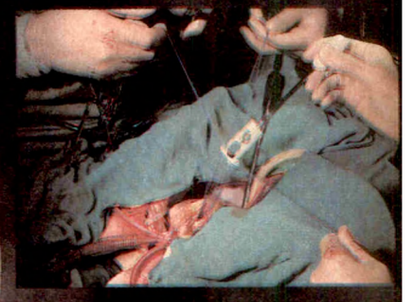
maintaining therapy

- usually 500 mg to 2.0 g daily in two to four doses
- maximum recommended daily dose is 3.0 g
- if effective control of blood pressure cannot be maintained on 2.0 g methyldopa daily and a thiazide is not already part of the regimen, a thiazide should be added
- occasional tolerance may occur, usually between the second and third month of therapy; adding a diuretic or increasing the dosage of ALDOMET frequently restores effective control
- patients with impaired renal function may respond to lower doses; syncope in older patients may be related to an increased sensitivity and advanced arteriosclerotic vascular disease and may be avoided by lower doses

Children

- initial dosage is based on 10 mg/kg of body weight daily in two to four doses
- increase or decrease daily dosage until adequate response is achieved
- maximum dosage is 65 mg/kg or 3.0 g daily, whichever is less

No Matter How You Look At It...



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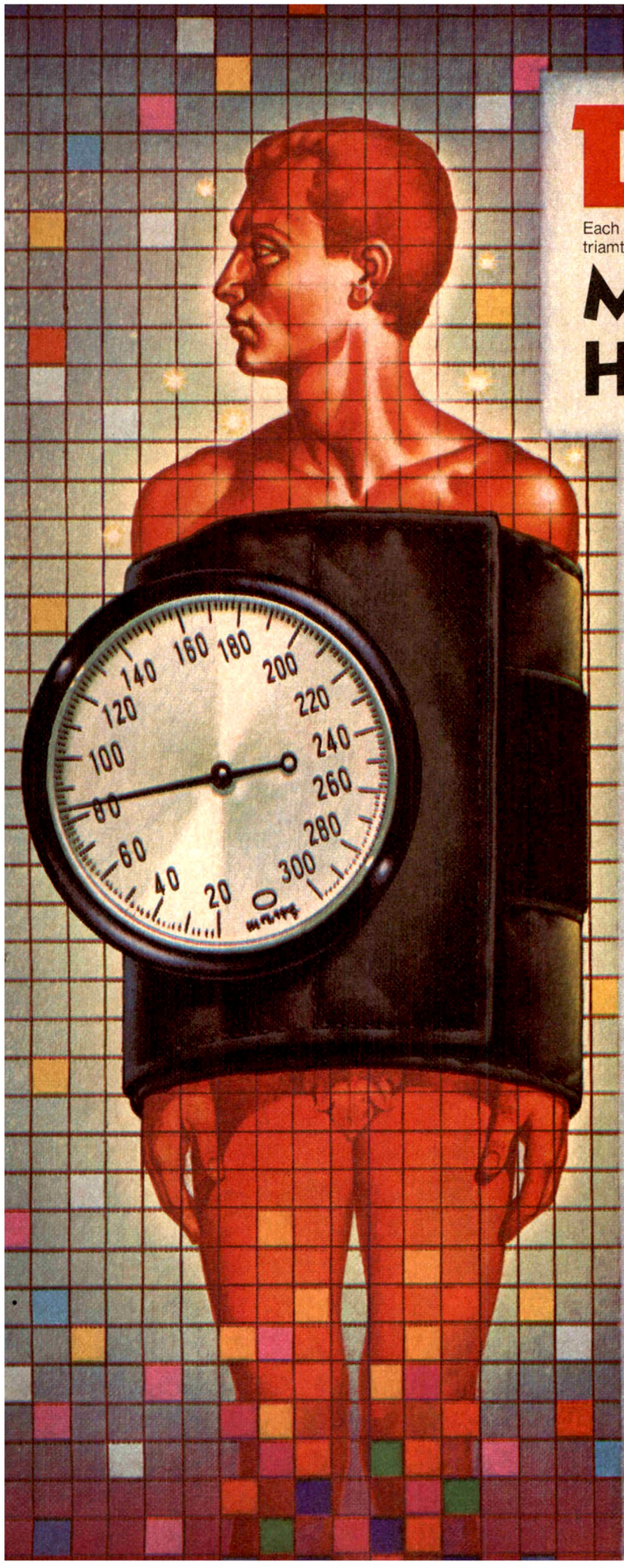

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Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K+ frequently; both can cause K+ retention and elevated serum K+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

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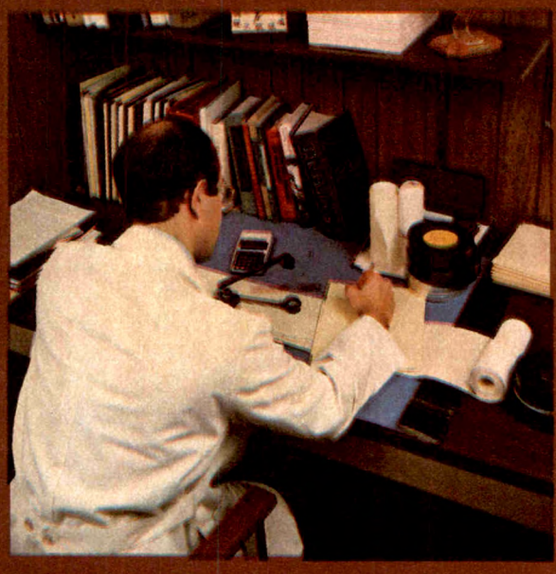
IF HE HAD THE E for M CATH LAB COMPUTER,



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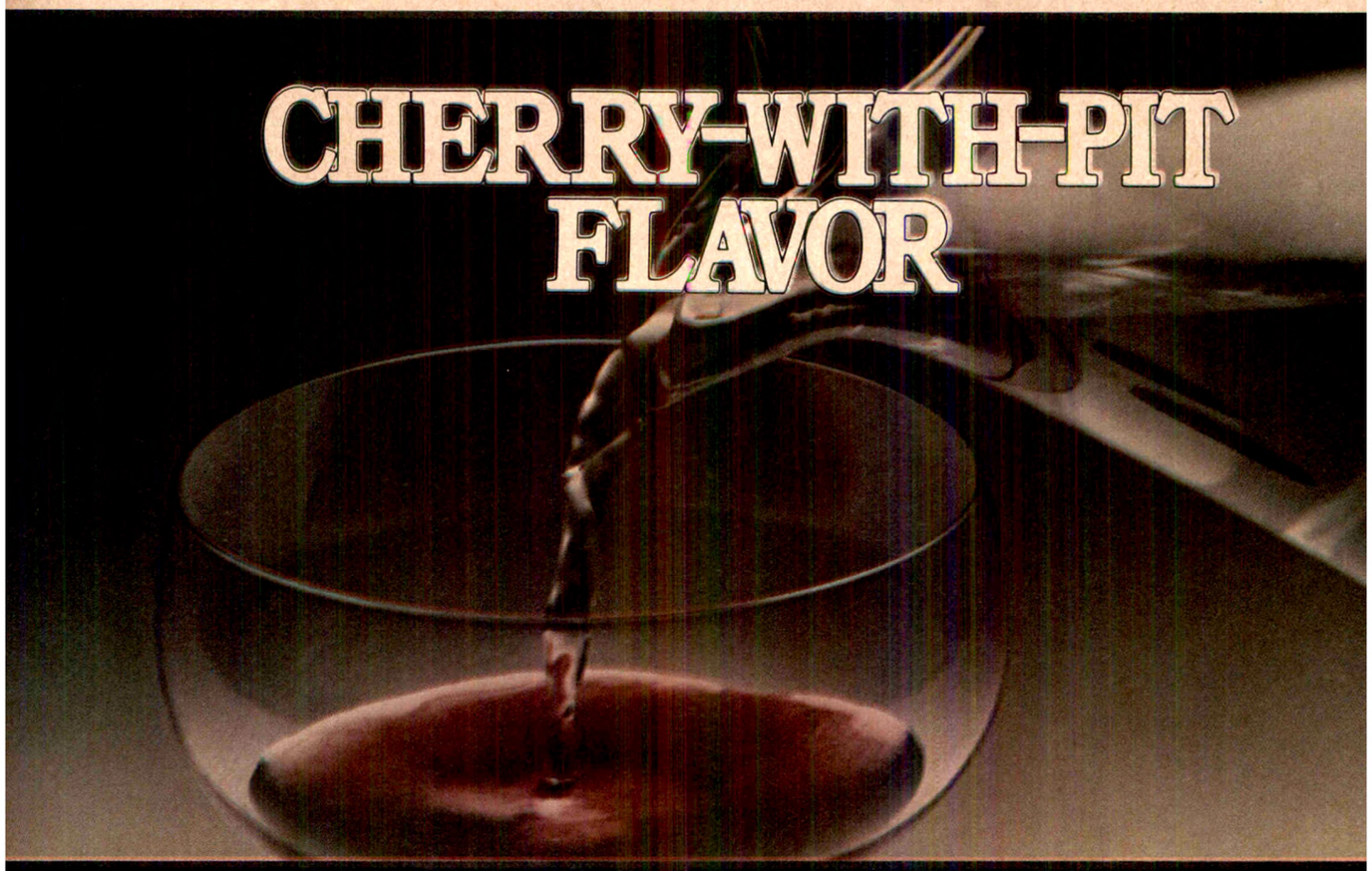

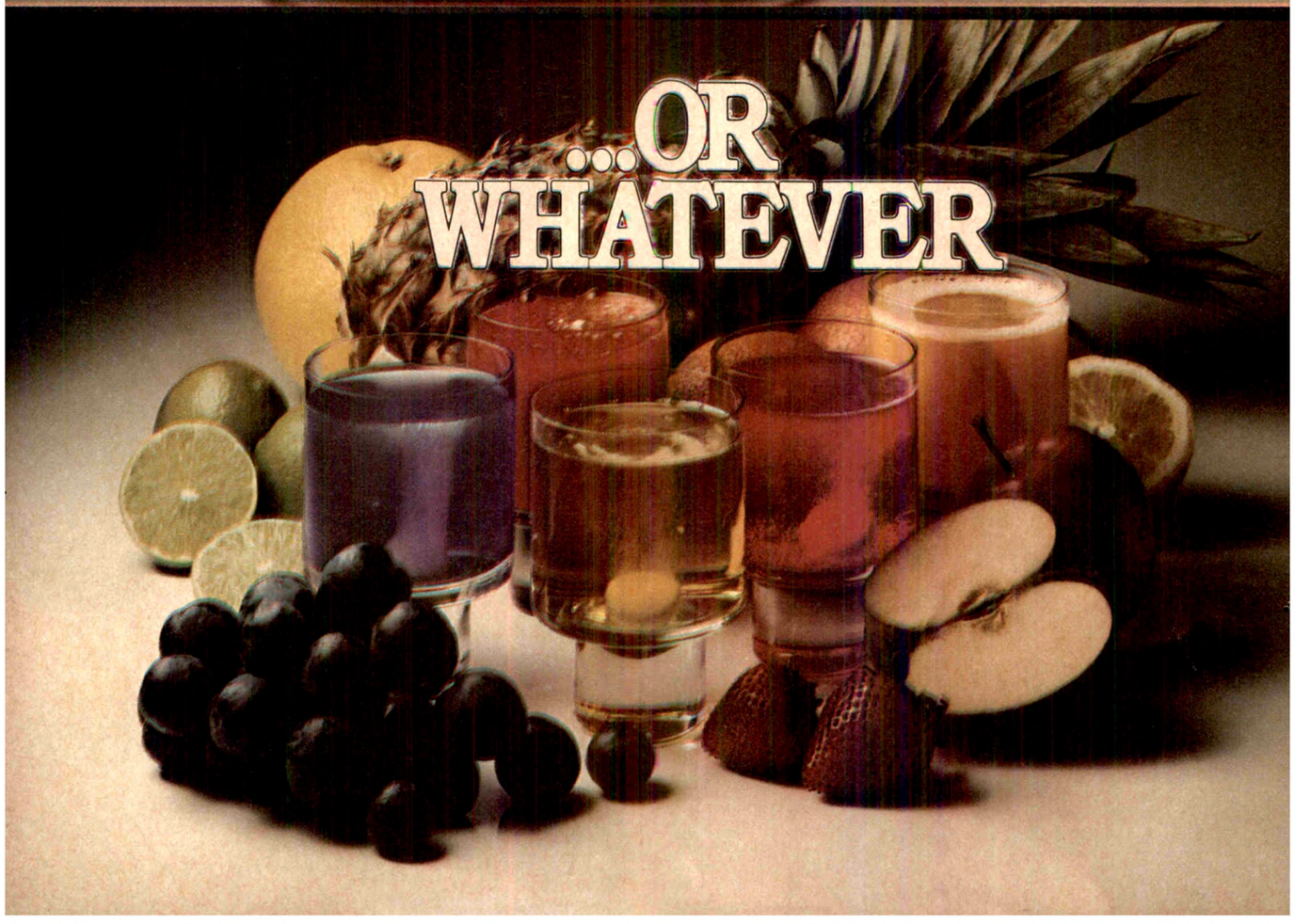

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Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

Indications: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

Contraindications: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements.

Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis.

High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest.

To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve each Klorvess Effervescent Tablet in 3 to 4 ounces of water or fruit juice, or dilute each tablespoonful of Klorvess (potassium chloride) 10% Liquid in 3 to 4 ounces of water. Both of these solutions should be ingested slowly with or immediately after meals.

Adverse Reactions: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts.

The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest.

The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

Dosage and Administration: Klorvess Effervescent Tablets: Adults—One Klorvess Effervescent Tablet (20 mEq each of potassium and chloride) completely dissolved in 3 to 4 ounces of cold water or fruit juice 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) of Klorvess Liquid (20 mEq of potassium chloride) completely diluted in 3 to 4 ounces of water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating. Deviations from these recommended dosages may be indicated in certain cases of hypokalemia based upon the patient's status. The average total daily dosage must be governed by the patient's response as determined by frequent evaluation of serum electrolytes, EKG and clinical status.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

Treatment of Hyperkalemia: 1. Dextrose solution, 10 or 25% containing 10 units of crystalline insulin per 20 g dextrose, given IV in a dose of 300 to 500 ml in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resins, orally and as retention enema. (Caution: Ammonium compounds should not be used in patients with hepatic cirrhosis.) 3. Hemodialysis and peritoneal dialysis. 4. The use of potassium-containing foods or medicaments must be eliminated. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

How Supplied: Klorvess Effervescent Tablets (white)—60 tablets (2 Rx units of 30 effervescent tablets each). Each tablet is individually foil wrapped. Klorvess (potassium chloride) 10% Liquid (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Tablets and Liquid are also available in institutional packaging as follows: Klorvess Tablets—30 and 1000 tablets; Klorvess Liquid—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

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*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information. FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.
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CLINICAL STUDIES

167 Thallium-201 Myocardial Perfusion Scintigraphy to Evaluate Patients After Coronary Bypass Surgery

BARRY H. GREENBERG, RICHARD HART, ELIAS H. BOTVINICK, JEFFREY A. WERNER, BRUCE H. BRUNDAGE, DAVID M. SHAMES, KANU CHATTERJEE and WILLIAM W. PARMLEY

In this evaluation of 27 patients after coronary bypass surgery, thallium-201 stress scintigraphy proved valuable when used alone in documenting the surgical results. It showed good sensitivity (77 percent), was highly specific for the diagnosis of coronary stenosis and was significantly more specific than the symptom of chest pain, giving excellent localizing information and adding to the accuracy of stress tests. In this series stress scintigraphy identified 50 percent of all instances of stenotic grafts or native vessels, or both. These results confirm that postoperative imaging can be used alone to predict accurately the extent of revascularization and graft patency.

177 Serial Myocardial Scintigraphy After a Single Dose of Thallium-201 in Men After Acute Myocardial Infarction

THOMAS C. SMITHERMAN, ROGER C. OSBORN, Jr. and KENNETH A. NARAHARA

Studying the patterns of thallium-201 redistribution into perfusion defects when serial scintigraphy is carried out immediately after myocardial infarction, the investigators found that such serial myocardial imaging can overcome some of the limitations of a single thallium-201 scintigram and help delineate ischemic from infarcted myocardium in the postinfarction period. Fourteen patients with a diagnosis on admission of probable acute myocardial infarction received thallium-201 a mean of 1.3 hours after admission to the coronary care unit. Imaging began 10 minutes after the thallium injection and was repeated 4 to 8 hours later. Results of scintigraphy with technetium-99m stannous pyrophosphate performed 3 to 7 days after admission were compared with those of thallium-201 scintigrams. Regardless of the direction of change in thallium-201 uptake between the serial studies, the thallium-201 defect seen in the repeat or reperfusion study corresponded most closely to the area of infarction defined with the pyrophosphate scan. The most likely explanation for these results is that transiently ischemic but not dead myocardium slowly extracted thallium-201 from the small amount of isotope present in the circulating blood during the 4 to 8 hour interval between the two scans.

183 Results of Aortocoronary Bypass Grafting in Patients With Subendocardial Infarction: Late Follow-Up

AGOP AINTABLIAN, ROBER I. HAMBY, DANIEL WEISZ, IRWIN HOFFMAN, CHOUDARY VOLETI and B. GEORGE WISOFF

These operative results in 28 patients with subendocardial infarction followed up postoperatively for a mean period of 29 months show that the mortality and perioperative morbidity in this group are no different from those of an equal number of patients with unstable or stable angina. The majority of patients were asymptomatic after surgery, and there were no hospital or late deaths. The ventricular contractile pattern improved in 37 percent of the patients, an incidence rate identical with that of the group with stable angina.

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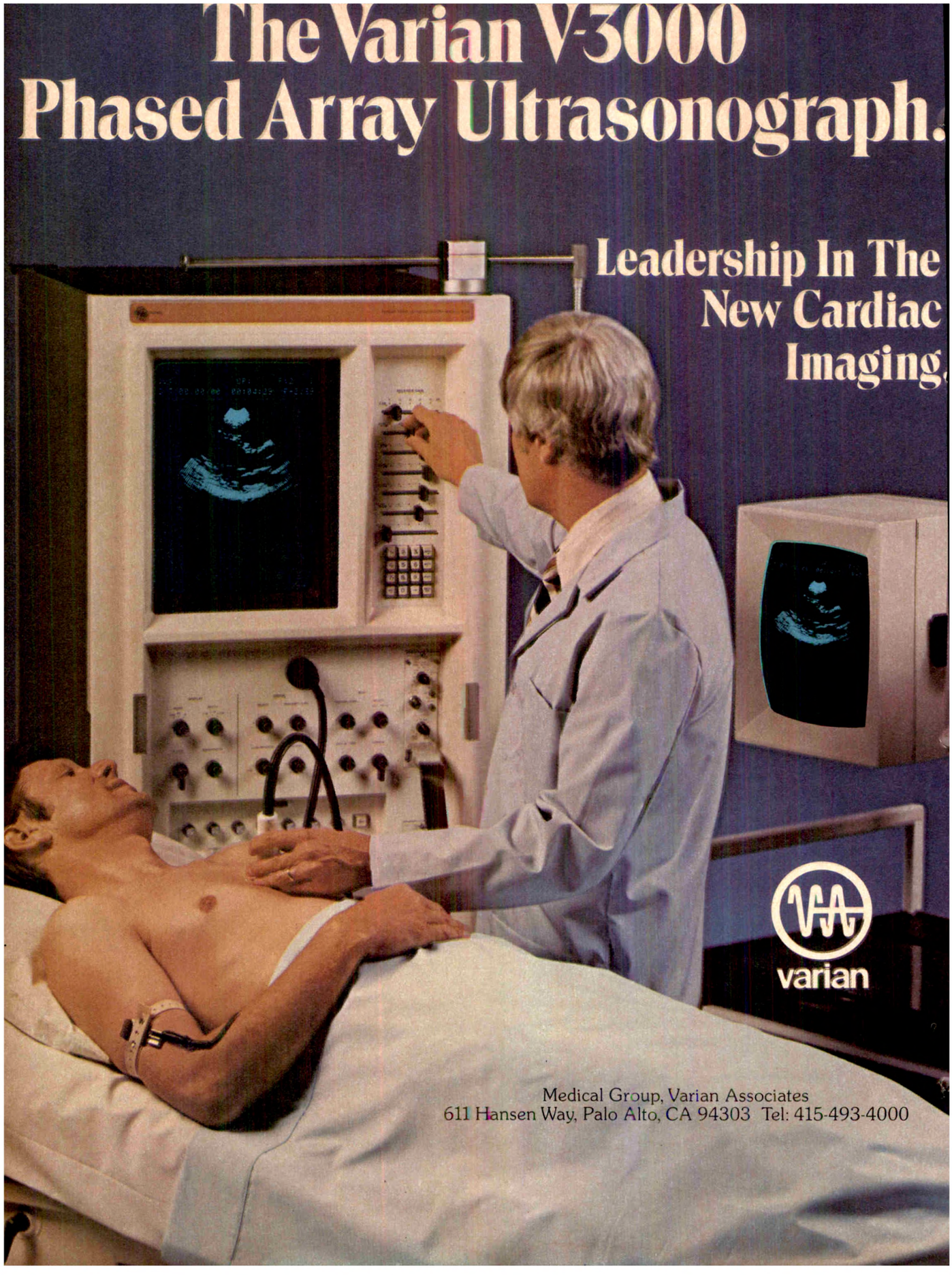
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187 Intraoperative Evaluation of the Functional Significance of Coronary Collateral Vessels in Patients With Coronary Artery Disease

WILLEM FLAMENG, FRANZ SCHWARZ and FRITZ W. HEHRLEIN

Intraoperative coronary hemodynamic studies in 65 patients undergoing aortocoronary bypass grafting show that under basal conditions a coronary stenosis must be at least 80 percent to be hemodynamically significant. Well developed collateral vessels produce in a completely occluded coronary artery hemodynamic changes that simulate those of a 90 percent coronary stenosis without collateral vessels. The data also demonstrate that coronary collateral vessels, identified angiographically as significant, compensate only partially for the coronary obstruction.

193 Effect of Coronary Stenosis on Myocardial Function, Ultrastructure and Aortocoronary Bypass Graft Hemodynamics

FRANZ SCHWARZ, WILLEM FLAMENG, KLAUS-ULRICH THIEDEMANN, WOLFGANG SCHAPER and MARTIN SCHLEPPER

This study in 70 patients with coronary artery disease showed no significant reduction of mechanical function and myocardial ultrastructure until 79 percent coronary artery stenosis occurred. With 80 to 89 percent stenosis, poststenotic vasodilation fully compensated for the stenosis. At 90 to 99 percent stenosis, vasodilatory compensation was inadequate, regional function decreased, degenerative ultrastructural alterations appeared and the fibrotic content of the myocardium increased. With complete occlusion compensation was ineffective, and severe loss of function and extensive scars developed. These results suggest that severe coronary lesions cause sequential changes in the morphologic features and function of the poststenotic myocardium and in themselves are an indication for operation.

202 Risk Stratification After Acute Myocardial Infarction

J. THOMAS BIGGER, Jr., CAREN A. HELLER, THOMAS L. WENGER, and FRANCIS M. WELD

In this study of 100 patients with acute myocardial infarction who lived 10 days after hospital admission and agreed to participate, the incidence of cardiac death in the 6 months after hospital discharge was almost four times greater than in the subsequent 6 months. Evaluating the predictive significance of variables for cardiac death within 6 months of acute myocardial infarction, these investigators did not find age a good predictor of early posthospital death after infarction. In descending order the univariates with the strongest association with mortality were blood urea nitrogen level, serum creatine level, serum uric acid level, enlarged heart 2 weeks after infarction, ventricular tachycardia 2 weeks after infarction, peak serum creatine kinase level and left ventricular failure in the coronary care unit. The odds of dying in the presence of one or more of these univariates are presented.

211 Clinicopathologic Analysis of Cardiac Dysfunction in 52 Patients With Sickle Cell Anemia

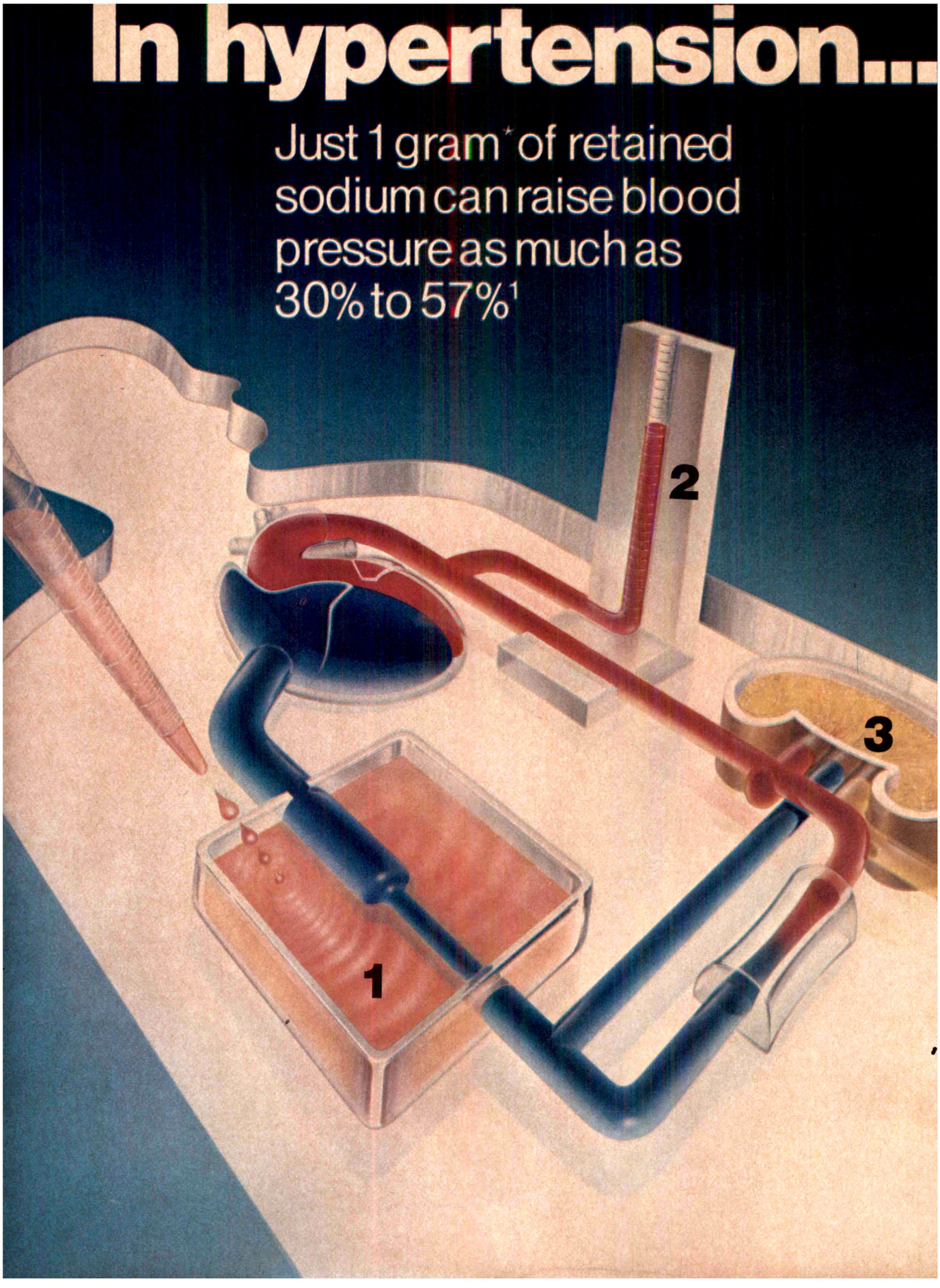
JOSEPH L. GERRY, Jr., BERNADINE H. BULKLEY and GROVER M. HUTCHINS

These data in 52 autopsy patients with sickle cell anemia do not support the concept of a specific "sickle cell cardiomyopathy" but indicate that cardiac dysfunction in such patients is due to the adverse effects of coexisting disease on the diminished cardiac reserve resulting from the chronic anemia. The average age of the patient at death was 17 years. Renal failure and infection were the most common causes of demise. Seventeen of the 52 patients had clinical evidence of congestive heart failure before death. Hypertensive cardiovascular disease associated with renal failure, cor pulmonale secondary to pulmonary hypertension and changes in blood volume associated with pregnancy and transfusion therapy explained most episodes of congestive heart failure in this study.

Continued on page A17

In hypertension...

Just 1 gram* of retained sodium can raise blood pressure as much as 30% to 57%[1]



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*All values given in this example are approximations based on standard physiologic data and solute-volume relationships.

†From a baseline of 80 mm. Hg diastolic.

BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema.

Contraindications: Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.

Warnings: Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.

Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

Adverse Reactions: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

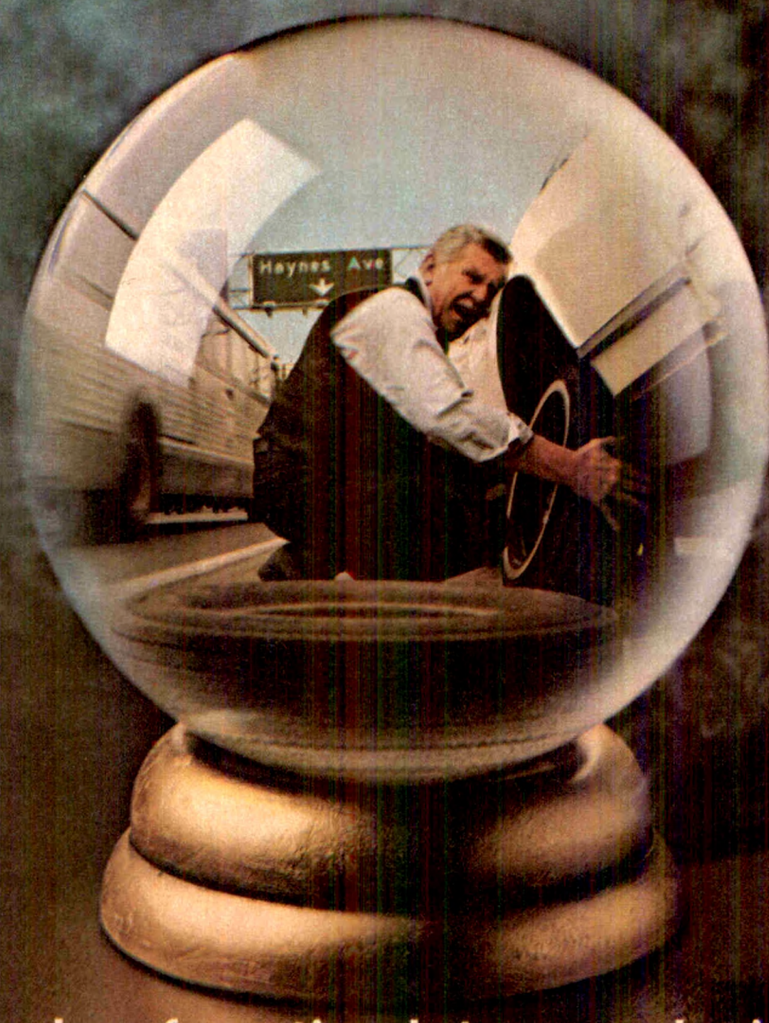
Usual Dose: One tablet daily.

How Supplied: Tablets—100 mg. (white, scored) and 50 mg. (aqua) in bottles of 100 and 1000; PAKs of 28 tablets, boxes of 6; unit-dose blister packs, boxes of 100 (10 x 10 strips).

References:

1. Guyton, A.C.: Regulation of arterial pressure: II. The renal-body fluid system for long-term pressure control. Mechanisms of hypertension, in Textbook of Medical Physiology, Philadelphia, Saunders, 1976, p. 281. **2.** Kaplan, N.: Treating hypertension: The results are in, in Mandates Hypertension (Kaplan, N.M., ed.), New York, Medcom, 1976, p. 6. **3.** Finnerty, F.A., Jr.: Hypertension: The Continuing Challenge, Scientific Exhibit, Meeting of AAFP, Boston, Mass., Sept. 20-23, 1976. **4.** Fries, E.D.: The treatment of hypertension: Why, when and how, in Hypertension Manual (Laragh, J.H., ed.), New York, Dun-Donnelley, 1974. p. 751. **5.** Tarazi, R.C.: Modern concepts in diuretic therapy, Postgrad. Med. 56:37, 1974.

Predictable angina*



...during episodes of emotional stress or physical exertion

SUMMARY OF PRESCRIBING INFORMATION

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Probably effective: The chewable dosage form of SORBITRATE is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.

Precautions: Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: *Individual Dose:* To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg.

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STUART PHARMACEUTICALS

CONTENTS

EXPERIMENTAL STUDIES

217 Prolonged Protective Effect of Propranolol on Hypoxic Heart Muscle

WINIFRED G. NAYLER, CARMEN E. YEPEZ, ELISABETH FASSOLD and ROBERTO FERRARI

Perfused propranolol-treated rabbit hearts subjected to hypoxia released creatine kinase and myoglobin more slowly, had a lower rate of increase of resting tension, maintained better mitochondrial respiratory activity and had a relatively slower rate of mitochondrial Ca^{++}-accumulating activity than control rabbit hearts. This protective effect of propranolol pretreatment, persisting up to 72 hours after the last dose of propranolol, was not accompanied by a change in tissue level of adenosine triphosphate, creatine phosphate or glycogen. These results favor the existence of a long-term protective effect of propranolol and support the concept of secondary consequences of beta adrenoreceptor blockade. This protection may be due partly to either reduced tyrosine hydroxylase activity or a protective effect on mitochondria, particularly with respect to Ca^{++}-accumulating activity.

226 Beneficial Effects of Propranolol and Digitalis on Contraction and S-T Segment Elevation After Acute Coronary Occlusion

SURRENDER RAINA, VIDYA S. BANKA, KODANGUDI RAMANATHAN, MONTY M. BODENHEIMER and RICHARD H. HELFANT

These experimental data obtained in 22 open chest dogs indicate that the combination of propranolol and digitalis favorably affects both tension and S-T segment abnormalities after acute coronary occlusion. In the nonischemic zone, all tension measurements decreased significantly after the administration of propranolol. This effect was readily reversed to near prepropranolol levels by ouabain administration. In the border zone all tension measurements decreased significantly after coronary ligation and decreased further after the administration of propranolol but increased after ouabain infusion. Central ischemic zone tension was unaffected by either agent alone or in combination. To the degree that these experimental data can be extrapolated to man, they support the utility of adding digitalis to the regimen when propranolol therapy is considered advisable in patients with acute coronary heart disease. They also suggest that digitalis may be efficacious in propranolol-treated patients with acute coronary heart disease who subsequently exhibit impending or overt left ventricular failure.

234 Regional Redistribution of Myocardial Blood Flow After Coronary Occlusion and Reperfusion in the Conscious Dog

FRANCIS C. WHITE, MAX SANDERS and COLIN M. BLOOR

Using radiolabeled microspheres to study regional myocardial blood flow in conscious dogs after occlusion and after occlusion and reperfusion, these investigators observed that blood flow within a developing myocardial infarct is redistributed during the first few hours after occlusion, but that total and regional reflow measured soon after reperfusion are poor predictors of the extent of tissue salvage. The extent of collateral circulation at the time of occlusion is a major determinant of the extent of the ensuing infarct after both permanent occlusion and reperfusion. After permanent coronary occlusion, the regional myocardial blood flow during the first few hours after occlusion correlated highly with the extent of necrosis several days later. However, in the reperfused myocardium this relation became more complicated. These data suggest that the initial amount of collateral flow received by the ischemic myocardium together with the work demand on the myocardium at the time are the most important predictors of subsequent tissue viability.

244 Servocontrolled Cardiac Assistance: The Effects of Left Ventricular to Aortic and Left Atrial to Aortic Assistance on Infarct Size

HILLEL LAKS, RICHARD A. OTT, JOHN W. STANDEVEN, JOHN W. HAHN, OLGA M. BLAIR and VALLEE L. WILLMAN

Left ventricular to aortic assistance proved superior to left atrial to aortic assistance in salvaging ischemic myocardium after the production of myocardial infarction by occlusion of the proximal left anterior descending coronary artery in dogs. A servocontrolled roller pump used to control pump speed according to left atrial pressure allowed reduction of left ventricular pressure to 38 percent of systemic levels and provided stable bypass for prolonged periods. Clinical application to patients after cardiac surgery is feasible.

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CONTENTS

251 Early Quantification of Experimental Myocardial Infarction With Technetium-99m Glucoheptonate: Scintigraphic and Anatomic Studies

DANIEL R. ALONSO, JEROME G. JACOBSTEIN, PAUL R. CIPRIANO, ARTHUR J. ROBERTS, MARIA L. ALONSO and SUSAN A. KLINE. *With the technical assistance of* EMILIO CAMPO and CAROLYN PAVLICK

Myocardial infact scintigraphy using technetium-99m glucoheptonate in 45 dogs with acute myocardial infarction revealed that scintigraphic infarct size correlated with infarct weight in anterior and inferior infarcts. Technetium-99m glucoheptonate also concentrated in a rim of myocardium around the infarct that probably represented the ischemic zone. Hyperosmotic mannitol perfusion and reperfusion greatly increased the uptake of technetium-99m glucoheptonate by the infarcted myocardium. This technique consistently detects early canine infarcts and provides a reliable estimate of their size by 6 hours after coronary occlusion.

PEDIATRIC CARDIOLOGY

259 Echocardiographic Features of Congenital Mitral Stenosis

DAVID J. DRISCOLL, HOWARD P. GUTGESELL and DAN G. McNAMARA

In this study of patients with congenital mitral stenosis, the echocardiographic findings included diastolic anterior motion of the posterior leaflet of the mitral valve, absence of the *A* wave and reduction of the E-F slope. Diastolic vibration of the mitral leaflets occurred in 21 of the 30 patients with mitral stenosis and in 8 of the 145 normal children but in none of the patients with coarctation of the aorta. Patients with severe mitral stenosis tended to have a greater decrease in E-F slope and exhibited abnormal motion of the posterior mitral leaflet more frequently than patients with only mild or moderately severe mitral stenosis. The mitral valve echogram was more useful in detecting the presence of congenital mitral stenosis than in determining the precise anatomy or severity of the mitral valve lesion.

REPORTS ON THERAPY

267 Combined Nitroprusside-Dopamine Therapy in Severe Chronic Congestive Heart Failure. Dose-Related Hemodynamic Advantages Over Single Drug Infusions

DALE R. STEMPLE, JAY H. KLEIMAN and DONALD C. HARRISON

Comparing the maximal hemodynamic improvement achieved with optimal doses of nitroprusside and dopamine singly and in combination in 13 patients with severe cardiac decompensation, these investigators show that the combination produced a significantly greater increase in cardiac output and physiologic improvement in overall circulatory function than either agent alone. The effect of these drugs on cardiac output is mediated largely by a change in systemic vascular resistance. In these patients cardiac output was quite sensitive to changes in impedance and relatively insensitive to changes in left ventricular filling pressure. These observations explain the effectiveness of nitroprusside in improving circulatory function and suggest that patients responding inadequately to higher infusion rates of dopamine may benefit more from the addition of a vasodilator agent to their therapy than from a further increase in the rate of dopamine infusion. According to these results, combined dopamine and nitroprusside therapy provides an excellent method of reversing refractory congestive heart failure in appropriately selected patients.

276 Human Electropharmacology of Tocainide, a Lidocaine Congener

LEONARD N. HOROWITZ, MARK E. JOSEPHSON and ARDESHIR FARSHIDI

In 10 patients with coronary artery disease, intravenously administered tocainide at blood levels effective against ventricular arrhythmias caused no statistically significant changes in sinus nodal recovery time, sinoatri-

Continued on page A20

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al conduction time, intraatrial conduction time, atrial, atrioventricular (A-V) nodal and ventricular refractory periods or intraventricular conduction time. Similarly, no adverse effects on A-V conduction were observed in patients with an intraventricular conduction disturbance or a prolonged control H-V interval. These results are not surprising because the effects of tocainide in suppressing enhanced automaticity may be exerted through alterations of membrane responsiveness, local conduction and refractoriness, alterations that cannot be assessed with electrophysiologic testing in man.

281 Recurrent Cardiac Tamponade and Large Pericardial Effusions: Management With an Indwelling Pericardial Catheter

JEANNE Y. WEI, GEORGE J. TAYLOR and STEPHEN C. ACHUFF

Satisfactory expriences in three patients illustrate the value of a new safe technique using an atraumatic indwelling catheter for the short-term management of large or rapidly reaccumulating pericardial effusions. This technique permits continuous pericardial fluid drainage, provides a convenient route for intrapericardial instillation of chemotherapeutic agents and may eliminate the need for surgery. This catheter system is superior to small bore tubing inserted through the aspiration needle because the catheter is larger, the multiple side holes make occlusion by viscous or hemorrhagic fluid less likely and the curved end is less likely to lacerate epicardial coronary vessels or provoke cardiac arrhythmias.

REVIEWS

283 Discrete Subaortic Stenosis in Adults

CHUNG-SHIN SUNG, EVERETT C. PRICE and DENTON A. COOLEY

Of 138 patients operated on for discrete subaortic stenosis, only 36 patients (26 percent) in this series were adults. The adult group had a high incidence rate of associated cardiac defects and bacterial endocarditis, and more adults than children were symptomatic. In patients without aortic regurgitation, the clinical findings were similar to those in patients with aortic valve stenosis. A systolic murmur, narrow pulse pressure and delayed and prolonged carotid upstroke were common findings. The usual criteria for diagnosis, localization of the gradient below the aortic valve at cardiac catheterization or angiographic demonstration of discrete subaortic stenosis, are not always evident. Echocardiography may help in the diagnosis by demonstrating early systolic closure of the aortic valve leaflets. Operative results in this group of patients indicate that discrete subaortic stenosis is not always easily relieved surgically. However, patients with a localized membrane and no other heart defects operated on early in life appear to have a better chance for excellent long-term results.

DIAGNOSTIC SHELF

291 Diagnosis of Dissecting Aortic Aneurysm With Suprasternal Echocardiography

WOLFGANG KASPER, THOMAS MEINERTZ, FRIEDRICH KERSTING, KLAUS LANG and HANJÖRG JUST

This interesting case report illustrates how the use of the suprasternal approach improved the echographic diagnosis of aortic arch dissection in a 33 year old woman with Marfan's syndrome and this complication. With suprasternal echocardiography it was possible to visualize within the aortic lumen an m-shaped pattern—the aortic intimal flap—moving downward to the posterior aortic wall during systole. In an interesting variant, the noncoronary cusp showed a marked bulging toward the posterior wall, suggesting involvement of the aortic valve ring by dissection. The echocardiographic findings were confirmed with aortic cineangiography and the intraoperative findings. Suprasternal echocardiography is of diagnostic value for two reasons: (1) It allows detection of isolated aortic arch dissection, and (2) in cases of extended dissection beginning in the ascending aorta, it can demonstrate involvement of the aortic arch.

Continued on page A22

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CASE REPORTS

295 Systemic Hypertension Complicating Tetralogy of Fallot: Effects of Antihypertensive Therapy

WILLIAM BENGE and CARL W. WHITE

This interesting case illustrates the hemodynamic contribution of increased systemic vascular resistance in tetralogy of Fallot and the need for extreme caution if aggressive antihypertensive therapy is attempted before the cardiac lesion is surgically corrected. The intravenous administration of nitroprussides for 5 minutes to decrease the elevated systolic pressure to normal during cardiac catherization precipitated severe systemic oxygen desaturation and loss of consciousness in a previously acyanotic 20 year old woman with tetralogy of Fallot, an associated atrial septal defect, severe hypertension and congestive heart failure. After surgical correction of the cardiac anomaly, the patient tolerated antihypertensive therapy well.

299 Shunt Flow and Pulmonary Hemodynamics During Labor and Delivery in the Eisenmenger Syndrome

JAY MIDWALL, HERBERT JAFFIN, MICHAEL V. HERMAN and JOEL KUPERSMITH

Physiologic and pharmacologic studies during labor and delivery in a 28 year old woman with the Eisenmenger syndrome showed that contractions of the uterus were associated with a decrease in the ratio of pulmonary to systemic blood flow (Qp/Qs) from 1.58 to 1.05 and to 0.83 when forceps were applied during the contractions. Therapeutic abortion is usually advisable in pregnant patients with the Eisenmenger syndrome. However, when pregnancy cannot be terminated in such a patient, she should be given high concentrations of oxygen and epidural anesthesia, and serial arterial blood gas determinations should be performed to detect changes in shunt flow during delivery.

304 Effect of Propranolol on Fetal Tachycardia in Diabetic Pregnancy

ARTHUR TEUSCHER, EMILIO BOSSI, PETER IMHOF, ERHARD ERB, FRANCO P. STOCKER and JANN W. WEBER

A daily dose of 160 mg of propranolol administered to a pregnant diabetic mother during the last 20 days of pregnancy reduced fetal tachycardia from 200 beats/min to 120 to 160 beats/min. During Cesarean delivery the child's neonatal blood level of propranolol was 20 percent of the maternal sample, which is greater than expected on the basis of animal experiments. Propranolol proved essential in maintaining a normal heart rate when the infant manifested postpartum paroxysmal supraventricular tachycardia. The cause of this tachycardia is unknown. No serious side effects occurred, although thrombocytopenia was noted at age 1 hour. The platelet count became normal within 1 week.

CONTROVERSIES IN CARDIOLOGY

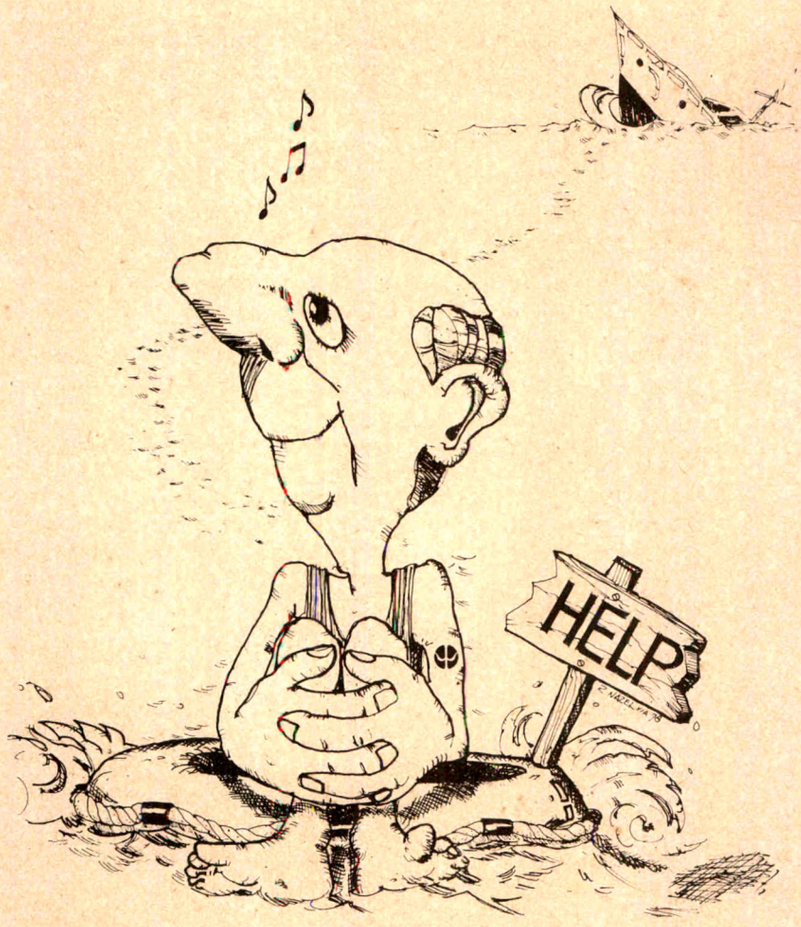
308 Value of Coronary Bypass Surgery. Controversies in Cardiology: Part I

J. WILLIS HURST, SPENCER B. KING III, R. BRUCE LOGUE, CHARLES R. HATCHER, Jr., ELLIS L. JONES, JOE M. CRAVER, JOHN S. DOUGLAS, Jr., ROBERT H. FRANCH, EDWARD R. DORNEY, B. WOODFIN COBBS, Jr., PAUL H. ROBINSON, STEPHEN D. CLEMENTS, Jr., JOEL KAPLAN and JAMES M. BRADFORD

There is sufficient scientific evidence that properly performed coronary bypass surgery will increase coronary blood flow, relieve angina pectoris completely in 60 percent and partially in 30 percent, and prolong the life of patients with obstruction of the left main artery, or triple or double vessel disease. Although there is no adequate evidence that such surgery will prolong the life of patients with single vessel obstruction, such individuals with unacceptable angina pectoris should be considered for bypass surgery, particularly those with obstruction of the left anterior descending coronary artery. A skilled surgical team operating on the appropriate patients may be expected to achieve a 1 percent hospital mortality rate, complete revascularization, a graft patency rate of 90 percent, a 4 to 6 percent perioperative infarction rate and a 90 to 95 percent 5 year cumulative patient survival rate. Because coronary bypass surgery increases coronary blood flow and propranolol decreases the oxygen requirement of the myocardium, it is appropriate and wise to use both in the same carefully selected patients.

Continued on page A24

[illegible] your p[illegible] ma[illegible]r patient misses his regular check up....



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CONTENTS

330 Influence of Myocardial Revascularization on Survival. Controversies in Cardiology: Part II

C. RICHARD CONTI

Although coronary bypass surgery can evidently be performed with low rates of morbidity and mortality and successfully reduce or eliminate symptomatic angina pectoris, the available data do not prove that the procedure prolongs life, except possibly in patients with angina pectoris resulting from left main coronary stenosis. The degree of permanent ventricular impairment is the most important determinant of survival in medically treated patients. When the degree of ventricular impairment is small, survival can be favorably influenced in medically treated patients, even in those with multiple vessel coronary artery disease. Thirty-six months after patients have been rejected for operation and treated medically, survival is significantly greater in patients with an ejection fraction of more than 35 percent than in those with an ejection fraction of less than 35 percent, regardless of the degree of coronary vessel involvement. A prospective long-term study of comparable patients is necessary if meaningful data are to be obtained to answer the important question of whether myocardial revascularization prolongs life.

SPECIAL DEPARTMENTS

333 Letters to the Editor

Veterans Administration Cooperative Study of Surgery for Coronary Arterial Occlusive Disease—I and II—J. S. Carey, R. A. Cukingnan, K. M. Detre, et al.

Congestive Heart Failure, Cardiomegaly and Embolism in Ischemic Heart Disease—W. P. Hood, Jr. and R. C. Hinton

336 American College of Cardiology News

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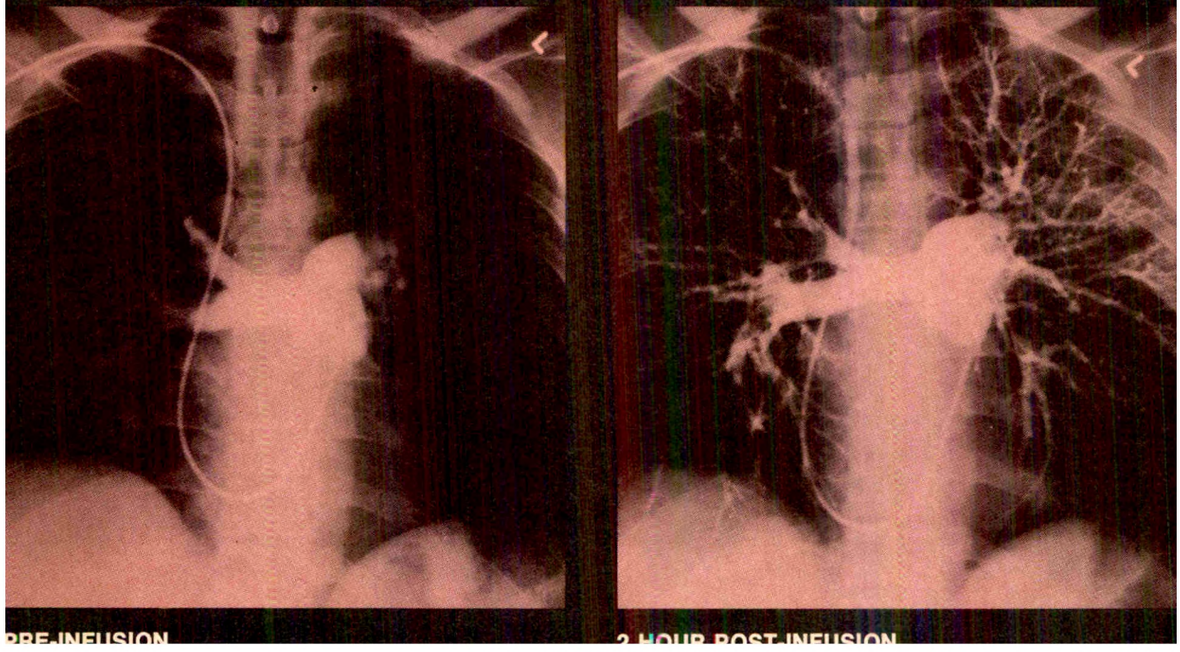

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Acute massive pulmonary embolism is a catastrophic phenomenon. It is estimated that between 140,000 and 200,000 persons die each year as a result of pulmonary embolism. Previously, anticoagulants or surgery have been the only measures available to the physician to combat this condition.

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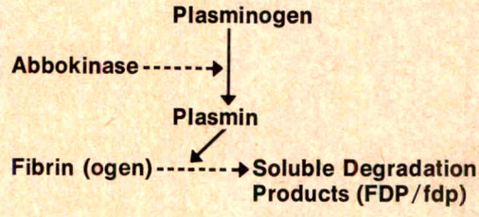

Diagrammatic representation of the activation of plasminogen by Abbokinase, and the degradation of fibrin (ogen) by plasmin.

A new generation of thrombolytic agents

Abbokinase acts on the endogenous fibrinolytic system by converting plasminogen to the proteolytic enzyme, plasmin. Plasmin, in turn, degrades fibrin clots as well as fibrinogen and other plasma proteins.[1] The plasmin is rapidly inactivated by a variety of naturally occurring plasma inhibitors.[2] Since plasminogen is present in the thrombus/embolus, activation by Abbokinase occurs within the thrombus/embolus as well as on its surface.[3]

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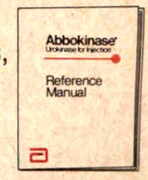

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References

1. McNicol, G. P., The Fibrinolytic Enzyme System, *Postgraduate Medicine*, August, 1973 (supplement). **2.** Aoki, N., et al, The Behavior of a 2-Plasmin Inhibitor in Fibrinolytic States, *Journal of Clinical Investigation*, 60:361-369, 1977. **3.** Chesterman, C. N., et al, Relationship of Plasminogen Activator to Fibrin, *Nature* (New Biol.), 238:15-17, 1972.

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Brief Summary

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8013241R

ABBOKINASE (urokinase for injection) should only be used by physicians with wide experience in the management of thrombotic disease in hospitals where the recommended clinical and laboratory monitoring (see WARNINGS, PRECAUTIONS and DOSAGE AND ADMINISTRATION) can be performed.

When considering treatment with urokinase, the physician should carefully assess the overall clinical status and history of the patient. The hemostatic capability of the patient is more profoundly altered and bleeding more frequent with urokinase therapy than with heparin or oral coumarin anticoagulant therapy. When bleeding occurs it is also more severe and more difficult to manage. The potential risk of serious hemorrhage relative to such factors as age, physical condition, and underlying bleeding tendency of the patient (as described under WARNINGS and PRECAUTIONS) should be weighed against the potential benefits of treating the patient with urokinase.

INDICATIONS

Pulmonary Embolism

ABBOKINASE (urokinase for injection) is indicated in adults:

for the lysis of acute massive pulmonary emboli, defined as obstruction or significant filling defects involving two or more lobar pulmonary arteries or an equivalent amount of emboli in other vessels.[8]

for the lysis of pulmonary emboli accompanied by unstable hemodynamics, i.e., failure to maintain blood pressure without supportive measures.

The diagnosis should be confirmed by objective means, preferably pulmonary arteriography.

Urokinase treatment should be instituted as soon as possible after onset of pulmonary embolism, and no later than five days after onset. Under these circumstances, angiographic and hemodynamic measurements demonstrate a more rapid improvement during the first 24 hours of therapy than with heparin therapy (Table I).[7-9] However, it has not been established that treatment with urokinase decreases morbidity or mortality, when compared to heparin therapy alone.

TABLE I †

	UPET*		USPET**	
	Heparin	12-Hour Urokinase	12-Hour Urokinase	24-Hour Urokinase
Change in angiographic severity score based on 4-point system	0.54	1.78	1.66	1.76
Decrease in relative percentage perfusion defect on lung scans	8.3	24.1	20	29.2
Change in pulmonary artery pressure (mm Hg)	−1.1	−6.2	−7.28	−7.53
Change in cardiac index (l/min/m²)	−0.05	+0.02	+0.06	+0.30

*Urokinase pulmonary embolism trial.
**Urokinase-streptokinase pulmonary embolism trial.

Evaluations were obtained between 18 and 30 hours after the start of therapy. After several days, there were no differences between the results in the heparin treated patients and those receiving urokinase.

† Adapted from (7).

CONTRAINDICATIONS — Because thrombolytic therapy increases the risk of bleeding, urokinase is contraindicated in the following situations:

1. Surgery within ten days. Liver or kidney biopsy, lumbar puncture, thoracentesis or paracentesis, extensive or multiple cutdowns should be considered surgical procedures.
2. Intraarterial diagnostic procedure within ten days.
3. Ulcerative wound.
4. Recent trauma with possibility of internal injuries.
5. Visceral or intracranial malignancy.
6. Pregnancy and the first ten days of the post-partum period.
7. Ulcerative colitis, diverticulitis or an actively bleeding lesion (or one with a significant potential for bleeding) of the gastrointestinal or genitourinary tract.
8. Severe hypertension.
9. Acute or chronic hepatic or renal insufficiency.
10. Uncontrolled hypocoagulable state, including one that may be caused by a coagulation factor deficiency, thrombocytopenia, spontaneous fibrinolysis, or another purpuric or hemorrhagic disorder.
11. Chronic lung disease with cavitation, e.g., tuberculosis.
12. Subacute bacterial endocarditis or rheumatic valvular disease.
13. Recent cerebral embolism, thrombosis or hemorrhage. Treatment with urokinase is contraindicated for at least two months after cerebral embolism, thrombosis or hemorrhage because patients with cerebral infarction remain at risk of bleeding into the infarcted tissue.
14. Any other condition in which bleeding might constitute a significant hazard or be particularly difficult to manage because of its location.

The conditions listed above should not be regarded as absolute contraindications. Rather, the risk of hemorrhage must be weighed carefully against the anticipated benefits of urokinase therapy in an individual patient and the benefits and risks associated with the use of urokinase should be compared to the benefits and risks associated with other forms of therapy.

WARNINGS

Bleeding

Activation of the fibrinolytic system with urokinase results in a more profound alteration of the hemostatic status of the patient than does anticoagulant therapy with heparin or coumarin agents. The aim of urokinase therapy is the production of sufficient amounts of plasmin for the lysis of intravascular deposits of fibrin; however, fibrin deposits which provide hemostasis, for example, at sites of needle punctures, are also destined for lysis, and bleeding from such sites may occur. The possibility of bruising or hematoma formation, especially with intramuscular injections, is high during thrombolytic therapy. Unnecessary handling of the patient should be avoided. Strict attention should be given to this section and the CONTRAINDICATIONS section in order to minimize the risk of bleeding.

Because of the high risk of hematoma formation, intramuscular injections must be avoided during urokinase therapy, as with heparin therapy. Bleeding at sites of recent invasive procedures may occur. Hence, arterial invasive procedures must also be avoided before and during treatment with urokinase. Should an arterial puncture be *absolutely* necessary, the femoral artery must be avoided and the radial or brachial artery used. It should be done carefully by a physician experienced in such a procedure. Pressure should be applied for at least 15 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding. Also, venipunctures should be performed as carefully and infrequently as possible. If the bleeding from an invasive site is not serious, treatment may be continued with appropriate clinical observation. Local measures, i.e., pressure, should be initiated immediately.

Spontaneous bleeding from internal sites (not accessible for pressure application) may also occur. The risk of spontaneous bleeding is greater in patients with pre-existing hemostatic defects, e.g., patients with histories suggestive of prior bleeding problems, with or without demonstrable abnormalities in platelet count, prothrombin time, partial thromboplastin time, or bleeding time. Such patients should be assessed carefully before initiating treatment with urokinase.

In addition to its fibrinolytic action, plasmin also degrades fibrinogen, Factor V, Factor VIII, and other proteins. The products of plasmin degradation of fibrinogen and fibrin (FDP/fdp) possess an anticoagulant effect. Bleeding may be difficult to control because of this anticoagulant effect.

Should serious spontaneous bleeding occur, the infusion of urokinase should be terminated immediately, and treatment instituted as described under ADVERSE REACTIONS.

Predisposition to Cerebral Embolism

Treatment with urokinase of patients with atrial fibrillation or other conditions in which there is possible risk of cerebral embolism may be hazardous because of the risk of bleeding into the infarcted area.

Use of Anticoagulants

Concurrent use of anticoagulants with urokinase is not recommended and may be hazardous. Before starting urokinase in patients being treated with heparin, the effects of heparin should be allowed to diminish with time. As a general rule, a thrombin time of *less than twice* the normal control value is adequate for starting urokinase infusions safely. Similarly, heparin should not be started following urokinase therapy until the thrombin time has returned to *less than twice* the normal control value.

Rethrombosis has been observed after termination of urokinase treatment. In order to minimize this risk, the use of intravenous heparin followed by oral anticoagulant therapy is considered a necessary adjunct following urokinase therapy (see DOSAGE AND ADMINISTRATION).

Use in Pregnancy

See CONTRAINDICATIONS.

Use in Children

Safety and effectiveness of urokinase therapy in children have not been established; therefore, treatment of such patients is not recommended.

PRECAUTIONS

Drug Interactions

Concurrent use of drugs that may alter platelet function, e.g., aspirin, indomethacin, and phenylbutazone, should be avoided. The interaction of ABBOKINASE (urokinase for injection) with other drugs has not been studied.

Laboratory Monitoring

In patients who have received heparin, the thrombin time should be measured prior to starting urokinase. (See WARNINGS.) Similarly, the thrombin time should be monitored following urokinase therapy prior to instituting heparin. (See DOSAGE AND ADMINISTRATION.) During urokinase administration, the levels of fibrinogen, plasminogen, Factor V, and Factor VIII are usually substantially diminished. Concomitantly, the level of fibrin(ogen) degradation products (FDP/fdp) is increased. The combination of reduced fibrinogen and increased FDP/fdp results in a prolongation of the thrombin time. While changes in any of these parameters may serve as confirmation of the existence of a lytic state, no adjustment of dosage should be made on the basis of these test results.

ADVERSE REACTIONS

Incidence and Management

Strict observance of the contraindications, warnings, and precautions to the use of urokinase is essential to minimize the incidence and severity of adverse effects.[7]

BLEEDING

Incidence

Where thrombolytic agents (streptokinase and urokinase) were used in the same controlled clinical trial, severe bleeding (patients receiving a transfusion of greater than two units of blood) was seen in 4 and 6%, respectively. Several fatalities due to cerebral hemorrhage have occurred during urokinase therapy.

Less severe spontaneous bleeding has been observed during urokinase treatment at approximately twice the frequency as that occurring during heparin therapy. Oozing of blood from sites of percutaneous trauma is frequent; hence, all invasive procedures, especially arterial punctures and intramuscular injections must be avoided and intravenous punctures kept to a minimum before and during treatment with urokinase.

A moderate decrease in hematocrit not accompanied by clinically detectable bleeding occurred in approximately one out of five patients treated with urokinase.

Management of Severe Bleeding

In case of serious bleeding, urokinase therapy must be discontinued. If blood loss has been large, packed red cells are indicated. Plasma volume expanders (other than Dextran) are indicated to replace blood volume deficit. If only whole blood is available, it may also be used. Although the use of aminocaproic acid (ACA, AMICAR®) in humans as an antidote for urokinase has not been documented, it may be considered if the hemorrhage is unresponsive to blood replacement. (See WARNINGS.)

ALLERGIC REACTIONS

Although urokinase is a protein of human origin, and *in vitro* tests with the drug, as well as intradermal test in humans, gave no evidence of induced antibody formation, the possibility of serious allergic reactions (including anaphylaxis) occurring with its use cannot be excluded. Relatively mild allergic reactions, e.g., bronchospasm and skin rash, were reported rarely.

FEVER

Febrile episodes occurred in approximately two to three out of 100 patients. A cause and effect relationship has not been established. Symptomatic treatment is usually sufficient to alleviate discomfort. The use of acetaminophen rather than aspirin is recommended.

DOSAGE AND ADMINISTRATION

Dosing

ABBOKINASE IS INTENDED FOR INTRAVENOUS INFUSION ONLY.

A priming dose of 2,000 I.U./lb (4,400 I.U./kg) of ABBOKINASE is given as the Abbokinase-Normal Saline admixture over a period of ten minutes. This is followed by a continuous infusion of 2,000 I.U./lb/hr (4,400 I.U./kg/hr) of ABBOKINASE (given as the Abbokinase-Normal Saline admixture) for 12 hours. The total volume of fluid administered should not exceed 200 ml.

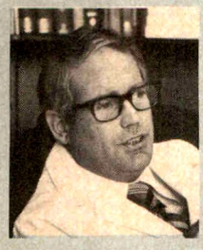
Administer ABBOKINASE (urokinase for injection) by means of a constant infusion pump that is capable of delivering a total volume of 195 ml.

Anticoagulation After Terminating Urokinase Treatment

At the end of urokinase therapy, treatment with heparin by continuous intravenous infusion is recommended. Heparin treatment should not begin until the thrombin time has decreased to *less than twice* the normal control value. See manufacturer's prescribing information for proper use of heparin.

Inner-View No. 2

A continuing educational series in Nuclear Cardiology



The interview excerpted here was conducted with Glen W. Hamilton, M.D., Chief, Nuclear Medicine Section, Veteran's Administration Hospital, Seattle, Washington. Dr. Hamilton is also an Associate Professor of Medicine, University of Washington School of Medicine.

Q. Of the nuclear cardiology studies available in clinical practice today, which are the most difficult to interpret?

A. Thallium images are probably the most difficult to interpret, and pyrophosphate are probably the next. In about 60% of all abnormal studies, the abnormality is quite obvious. The remaining 40% are quite difficult to read. As the physician gains experience, he will be able to read about half of those with confidence, but about 20% of all thallium studies remain difficult to interpret. Experienced observers will have legitimate disagreement as to whether a given study is normal or abnormal.

Q. Which of these tests are generally the best in the assessment of left ventricular function? Is this also the best study for assessing wall motion?

A. The multiple gated blood pool study yields the greatest clinical information compared to the difficulty of performing the test and, therefore, is the one we use in our clinical practice when we wish to assess a patient's ventricular function. The best study for assessing wall motion is probably the multiple gated study. It is not perfect, in that the right ventricle and the left ventricle overlap in all but the LAO view... but for most laboratories it is the most practical way to assess wall motion.

Q. What studies would you recommend to a nuclear physician or cardiologist beginning nuclear cardiology in a community hospital?

A. I would recommend two studies: multiple gated blood pool studies, and thallium imaging. The ventricular function measurements obtained from multiple gated studies are useful not only in patients who have suspected coronary disease, but also in a wide variety of other patients, such as people with lung disease, older patients who have undetected ventricular dysfunction, or presurgical patients. Clearly, this is going to be the largest volume study, and that's the place where they should start. After doing resting ventricular function studies, they should progress to thallium imaging. Six months from now, there should be enough data available on rest/exercise ventricular function studies using multiple gated imaging to indicate whether this technique is of general usefulness.

Q. Which studies are most difficult to perform?

A. Pyrophosphate studies are obviously the simplest to perform. The multiple gated blood pool study is performed quite simply. However, the equipment required is not present in every laboratory at the present time. Thallium, being a less ideal isotope, is probably the most difficult study, in terms of the technique required to achieve good diagnostic results.

Q. What may be the single most important use of these nuclear cardiology studies in five years?

A. First, I'm confident we will be noninvasively measuring ventricular function in a wide range of patients with various disease states — coronary artery disease, cardiomyopathy, chronic lung disease, valvular heart disease and many others. We will be able to follow these patients, correctly select the optimal time for surgical intervention, and alter medical therapy so that treatment is optimal. There's no question that this will happen. Secondly, if these tests turn out to be quite sensitive for the detection of coronary artery disease in its early presymptomatic stages, it may be possible to alter that disease by various interventions. This could become a very important national endeavor which could have far-ranging effects on health in this country.

Q. How widespread do you see these techniques becoming?

A. The need for studies of ventricular function will be comparable to the need for lung or bone scans. I really expect that most existing nuclear medicine laboratories, and, generally any hospital of two or three hundred beds, will be able to perform ventricular function studies within the next several years.

For the complete transcript of this interview with Dr. Hamilton, write Inner-View, General Electric Company, Medical Systems Division, P.O. Box 414 (Mail Code W-504), Milwaukee, WI 53201.

General Electric Medical Systems, Milwaukee, Toronto, Madrid.

GENERAL ELECTRIC

How does the number of insomniacs in your practice compare with the average in your specialty?

Results of a survey conducted among physicians[1]

family practice **12.8%**	cardiology and gastroenterology **18.3%***	internal medicine **17.5%**
neurology **14.1%**	ob/gyn **11.6%**	psychiatry **33.2%**
		surgery **16.4%**

	Insomnia	Hypersomnia	Narcolepsy	Enuresis	Somnambulism	Nightmares	Night Terrors
Family practice	12.8%	2.8%	0.9%	1.9%	1.0%	3.3%	1.5%
Cardiology and Gastroenterology*	18.3	3.5	0.6	0.9	1.1	4.7	1.3
Internal medicine	17.5	3.4	1.0	1.3	1.3	4.0	1.8
Neurology	14.1	2.8	1.6	3.0	1.5	4.2	2.3
Obstetrics and gynecology	11.6	4.7	1.6	1.7	1.7	4.1	2.1
Psychiatry	33.2	6.2	1.1	3.6	2.3	11.1	3.7
Surgery	16.4	4.9	1.2	4.2	1.3	4.3	3.6

Percentage of patients with sleep disorders, by specialty[1]

Regardless of specialty, the largest number of patients complaining of sleep disorders have insomnia: trouble falling asleep, difficulty staying asleep, early morning awakening, or some combination of these symptoms.

*Results for these specialties were not reported separately in the survey.[1]

How do other hypnotics compare with the leading medication for insomnia? While all drugs studied showed some efficacy in improving sleep during initial and short-term administration, they did not necessarily show statistical significance in all parameters measured.[2,3]
The agent printed in red is the leading medication for insomnia.

	statistically significant efficacy averaged for **NIGHTS 1-3**			statistically significant efficacy averaged for **NIGHTS 12-14**		
HYPNOTIC AGENT	time needed to fall asleep	time awake after sleep onset	total wake time	time needed to fall asleep	time awake after sleep onset	total wake time
chloral hydrate 1 Gm	NO	NO	NO	NO	NO	NO
ethchlorvynol 500 mg	NO	NO	NO	NO	NO	NO
DALMANE (flurazepam HCl) 30 mg	YES*	YES*	YES†	YES†	YES*	YES†
glutethimide 500 mg	NO	NO	NO	NO	NO	NO
methaqualone 250 mg	NO	YES*	NO	NO	NO	NO
methaqualone 400 mg	NO	NO	YES*	NO	NO	NO
pentobarbital 100 mg	NO	YES†	YES†	NO	NO	NO
secobarbital 100 mg	NO	YES*	YES†	NO	NO	NO
experimental hypnotic	NO	YES*	YES*	NO	NO	NO

*$P<0.05$
†$P<0.01$

The model of hypnotic efficacy

DALMANE®
(flurazepam HCl) C IV
30-MG AND 15-MG CAPSULES

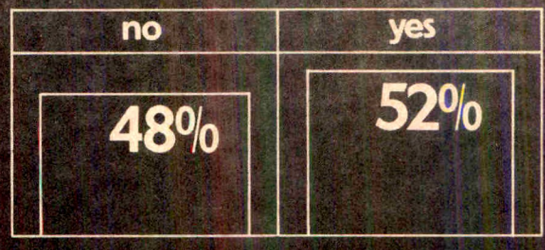
Dalmane may be used for patients on chronic warfarin therapy: no unacceptable fluctuation in prothrombin time has been reported.[4,5]

ROCHE

Please see following page for a summary of product information

It may be that some of your patients are not mentioning their insomnia to you.

When insomniacs were asked in a survey* if they consulted a physician about their sleep problems, they replied:



When a hypnotic is indicated

DALMANE®
(flurazepam HCl)

One 30-mg capsule *h.s.*—usual adult dosage
(15 mg may suffice in some patients).
One 15-mg capsule *h.s.*—initial dosage for elderly or debilitated patients.

Before prescribing Dalmane (flurazepam HCl), please consult complete product information, a summary of which follows:
Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.
Contraindications: Known hypersensitivity to flurazepam HCl.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).
Usage in Pregnancy: **Several studies of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) suggest increased risk of congenital malformations during the first trimester of pregnancy. Dalmane, a benzodiazepine, has not been studied adequately to determine whether it may be associated with such an increased risk. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
Not recommended for use in persons under

psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.
Precautions: In elderly and debilitated, limit initial dosage to 15 mg to preclude oversedation, dizziness and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.
Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations,

stimulation and hyperactivity, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase.
Dosage: Individualize for maximum beneficial effect.
Adults: 30 mg usual dosage; 15 mg may suffice in some patients.
Elderly or debilitated patients: 15 mg initially until response is determined.
Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

REFERENCES: 1. Kales A: *Med World News* 16: 29-44, Apr 5, 1976. 2. Kales A, *et al: J Clin Pharmacol* 17: 207-213, Apr 1977. 3. Kales A, *et al: Clin Pharmacol Ther* 18: 356-363, Sep 1975. 4. Robinson DS, Amidon EL: Interaction of benzodiazepines with warfarin in man, in *The Benzodiazepines*, edited by Garattini S, Mussini E, Randall LO. New York, Raven Press, 1973, p. 641. 5. Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ. 6. Dement WC: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ

*Call-in telephone survey directed at self-diagnosed insomniacs in the San Francisco Bay area, conducted by the Stanford University Sleep Disorders Clinic. Number of respondents: 523.[6]

ROCHE
ROCHE PRODUCTS INC.
Manati, Puerto Rico 00701

In cardio-diagnostic procedure, detail is everything, and the key to detail in ultrasound scanners, is resolution. The finer the resolution, the clearer the detail, and the easier it is to make an accurate diagnosis of a cardiac condition.

Our new heart dedicated Sonolayergraph SSH-10A is unsurpassed when it comes to resolution, providing an ultrafine diagnostic image.

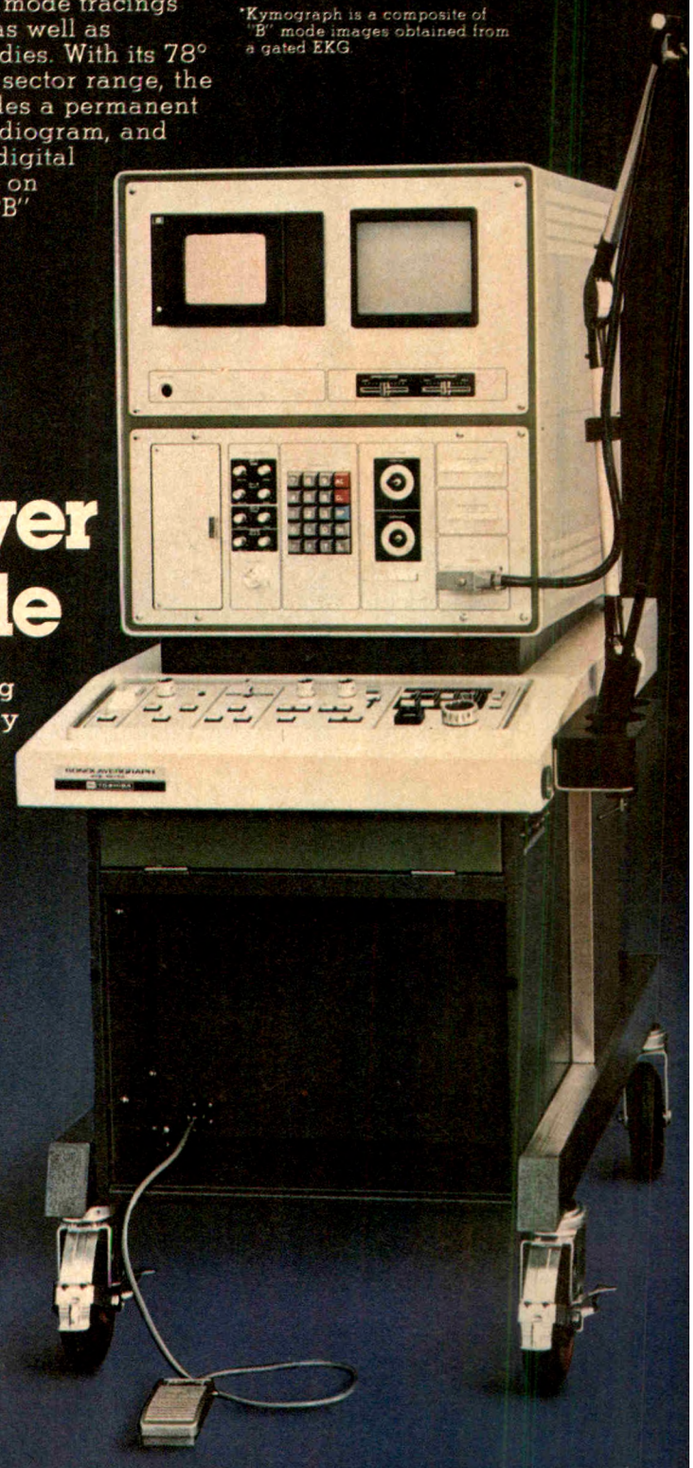
The SSH-10A Sonolayergraph represents the state-of-the-art in highly advanced high speed ultrasonic electronic scanners. A real time cross sectional, two-dimensional "B" mode image of the heart structure can be clearly obtained by positioning the probe on the chest wall. Valve movements, chamber size and detail of the internal structures of the heart can be clearly observed, measured and diagnosed. The SSH-10A is also capable of obtaining two "M" mode tracings simultaneously as well as Kymograph* studies. With its 78° true wide angle sector range, the SSH-10A provides a permanent EKG, phono-cardiogram, and patient ID with digital caliper read-out on the CRT in the "B" mode. The two angles of the "M" mode can also be easily displayed independently on a second CRT and/or strip recorder. Additionally, the "M" mode provides four channels of physiological monitoring, EKG, phono-cardiogram, carotid pulse and apex pulse.

When it comes to providing an accurate picture of your patient's heart condition, there are two things to remember, resolution and Toshiba.

*Kymograph is a composite of "B" mode images obtained from a gated EKG.

Details about he heart you never thought possible

Toshiba's dedicated heart ultrasound, featuring ultrafine resolution and electronic phased array in real time images



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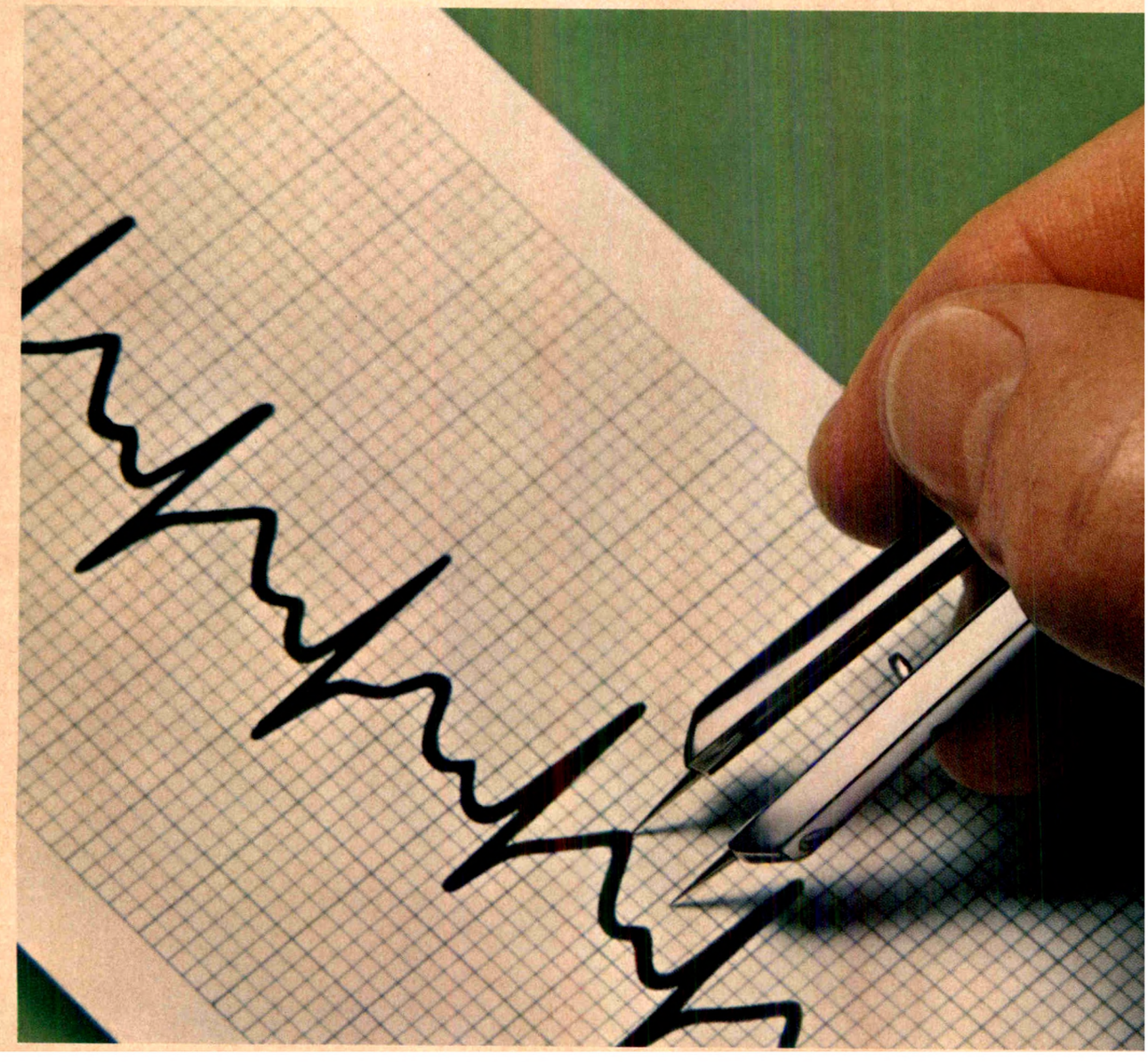
INDERAL®
(propranolol hydrochloride)
PERFORMANCE IN CARDIAC ARRHYTHMIAS

EFFECTIVE ALONE OR IN COMBINATION



INDERAL (propranolol hydrochloride): Successful treatment of supraventricular arrhythmias for over 10 years

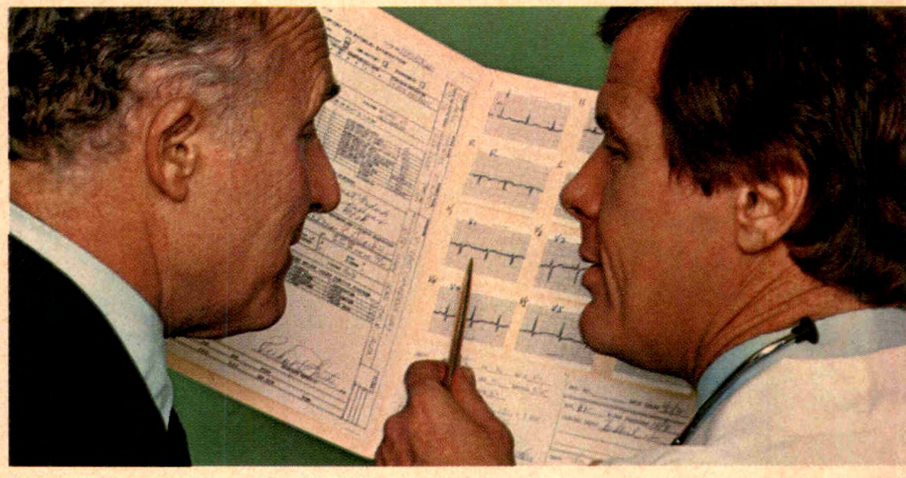
INDERAL, used alone or in combination with other antiarrhythmics, has improved or resolved a variety of supraventricular arrhythmias.[1-7]

INDERAL alone: Results of use against atrial tachyarrhythmias in one series have recently been reported:

Arrhythmia	Patients	Proportion deriving benefit	
		Complete	Partial
Sinus tachycardia	86	59%	22%
Atrial tachycardia (including paroxysmal type)	154	61%	19%
Atrial flutter	50	54%	32%
Atrial fibrillation	139	53%	26%

Adapted from Coodley and Snyder.[8]

INDERAL is particularly effective in therapy of supraventricular tachyarrhythmias.[9] It slows depolarization of sinus and ectopic pacemaker cells, and retards impulse-conduction in the atria and across the AV node.[1,10,11] In cases where it cannot restore normal sinus rhythm, INDERAL is frequently effective in reducing the ventricular rate.[1-3,12-14] INDERAL may prevent recurrent supraventricular tachyarrhythmias when digitalis and quinidine fail to do so.[9,12] In addition, INDERAL is a useful short-term adjunct for arrhythmias of thyrotoxicosis, when



used with specific therapy. Since INDERAL may mask the clinical signs of hyperthyroidism, abrupt withdrawal should be avoided to prevent exacerbation of the symptoms of hyperthyroidism.

And in combination: INDERAL has also been used to complement the actions of other antiarrhythmic agents.[3-5,8,9,13] The combination of INDERAL and quinidine has suppressed supraventricular arrhythmias that have not responded to either drug alone.[3,9]

When toxic doses of digitalis glycosides occasionally fail to control the ventricular rate in patients with atrial fibrillation or flutter, addition of INDERAL to a digitalis glycoside, with reduction of the digitalis dosage, may prolong AV conduction to the point where satisfactory control of ventricular rhythm is established.[8,15]

INDERAL: Often effective in tachyarrhythmias of digitalis intoxication[2,9,10,14] INDERAL has been found useful in the treatment of certain digitalis-induced arrhythmias that persist following discontinuation of digitalis and correction of electrolyte disturbances, particularly hypokalemia. Its use in this setting may be limited by the presence of significant congestive failure or heart block, and the development of severe bradycardia. (Please see prescribing information on the next page for "Overdosage or Exaggerated Response.")

INDERAL is contraindicated in sinus bradycardia, greater than first degree heart block, and congestive heart failure unless the failure is secondary to tachyarrhythmias treatable with INDERAL. (See prescribing information for complete list of CONTRAINDICATIONS.)

Please see next page for prescribing information.

Ayerst

BRIEF SUMMARY
(For full prescribing information, see package circular.)

INDERAL® Brand of propranolol hydrochloride

A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS: INDERAL is a beta-adrenergic receptor blocking drug, possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available beta receptor sites. When access to beta receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and one-half hours. The biologic half-life is approximately two to three hours. Propranolol is not significantly dialyzable. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade and this appears to be its principal antiarrhythmic mechanism of action. The membrane effect also plays a role, particularly, some authorities believe, in digitalis-induced arrhythmias. Beta-adrenergic blockade is of unique importance in the management of arrhythmias due to increased levels of circulating catecholamines or enhanced sensitivity of the heart to catecholamines (arrhythmias associated with pheochromocytoma, thyrotoxicosis, exercise).

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential and depresses cardiac function.

INDICATIONS: Cardiac Arrhythmias:

1.) Supraventricular arrhythmias
a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.)
b) Persistent sinus tachycardia which is noncompensatory and impairs the well-being of the patient.
c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy.
May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS.)
d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures.
e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

2.) Ventricular tachycardias
Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias.
a) Ventricular tachycardias
With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice. In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered. If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly. (See DOSAGE AND ADMINISTRATION.) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.*
b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

3.) Tachyarrhythmias of digitalis intoxication
If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur. (See OVERDOSAGE OR EXAGGERATED RESPONSE.)
Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION.)

4.) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia
Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, INDERAL may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. (See WARNINGS.)

Hypertrophic Subaortic Stenosis: INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of INDERAL in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.

Pheochromocytoma: After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use INDERAL (propranolol hydrochloride) unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS: INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS: CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely. a) If cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS: Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS: *Cardiovascular:* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DOSAGE AND ADMINISTRATION: The dosage range for INDERAL (propranolol hydrochloride) is different for each indication.

ORAL

ARRHYTHMIAS—10-30 mg three or four times daily, before meals and at bedtime.

HYPERTROPHIC SUBAORTIC STENOSIS—20-40 mg three or four times daily, before meals and at bedtime.

PHEOCHROMOCYTOMA—*Preoperatively*—60 mg daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.

—*Management of inoperable tumor*—30 mg daily in divided doses.

PEDIATRIC DOSAGE: At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS: Intravenous administration is reserved for life-threatening arrhythmias or those occurring under anesthesia. The usual dose is from 1 to 3 mg administered under careful monitoring, *e.g.*, electrocardiographic, central venous pressure. The rate of administration should not exceed 1 mg (1 ml) per minute to diminish the possibility of lowering blood pressure and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the site of action even when a slow circulation is present. If necessary, a second dose may be given after two minutes. Thereafter, additional drug should not be given in less than four hours. Additional INDERAL should not be given when the desired alteration in rate and/or rhythm is achieved.

Transference to oral therapy should be made as soon as possible.

The intravenous administration of INDERAL has not been evaluated adequately in the management of hypertensive emergencies.

OVERDOSAGE OR EXAGGERATED RESPONSE:

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg). IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY.

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS.

HYPOTENSION—VASOPRESSORS, *e.g.*, LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE.

HOW SUPPLIED: INDERAL (propranolol hydrochloride)

TABLETS

No. 461—Each scored tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 462—Each scored tablet contains 20 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 464—Each scored tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 468—Each scored tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

INJECTABLE

No. 3265—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 ml ampuls in boxes of 10.

REFERENCES: 1. Shand, D.G.: N. Engl. J. Med. *293*:280 (Aug. 7) 1975. 2. Conn, R.D.: Postgrad. Med. *55*(No. 2):131 (Feb.) 1974. 3. Fors, W.J., Vanderank, C.R., and Reynolds, E.W.: Am. J. Cardiol. *27*:190 (Feb.) 1971. 4. Levi, G.F., and Proto, C.: Cardiology *55*:249, 1970. 5. Stern, S.: Am. Heart J. *74*(No. 2):170 (Aug.) 1967. 6. Luria, M.H., Adelson, E.I., and Miller, A.J.: Circulation *34*:767 (Nov.) 1966. 7. Gianelly, R.E., Griffin, J.R., and Harrison, D.C.: Ann. Intern. Med. *66*:667 (Apr.) 1967. 8. Coodley, E.L., and Snyder, S.: Am. Fam. Physician *14*(No. 5):146 (Nov.) 1976. 9. Miller, R.R., Amsterdam, E.A., and Mason, D.T.: Drug Therapy *5*:110 (Feb.) 1975. 10. Danahy, D.T., and Aronow, W.S.: Postgrad. Med. *61*(No. 1):113 (Jan.) 1977. 11. Gettes, L.S.: Med. Opinion *5*(No. 9):19 (Sept.) 1976. 12. Gianelly, R.E., and Harrison, D.C.: Geriatrics *25*:120 (Apr.) 1970. 13. Michaelson, S.P., and Wolfson, S.: Cardiovasc. Med. *1*(No. 3):213 (Nov.) 1976. 14. Wit, A.L., Hoffman, B.F., and Rosen, M.R.: Am. Heart J. *90*(No. 5):665 (Nov.) 1975. 15. Bigger, J.T., and Giardina, E.G.V.: Cardiovasc. Clin. *6*(No. 2):103, 1974.

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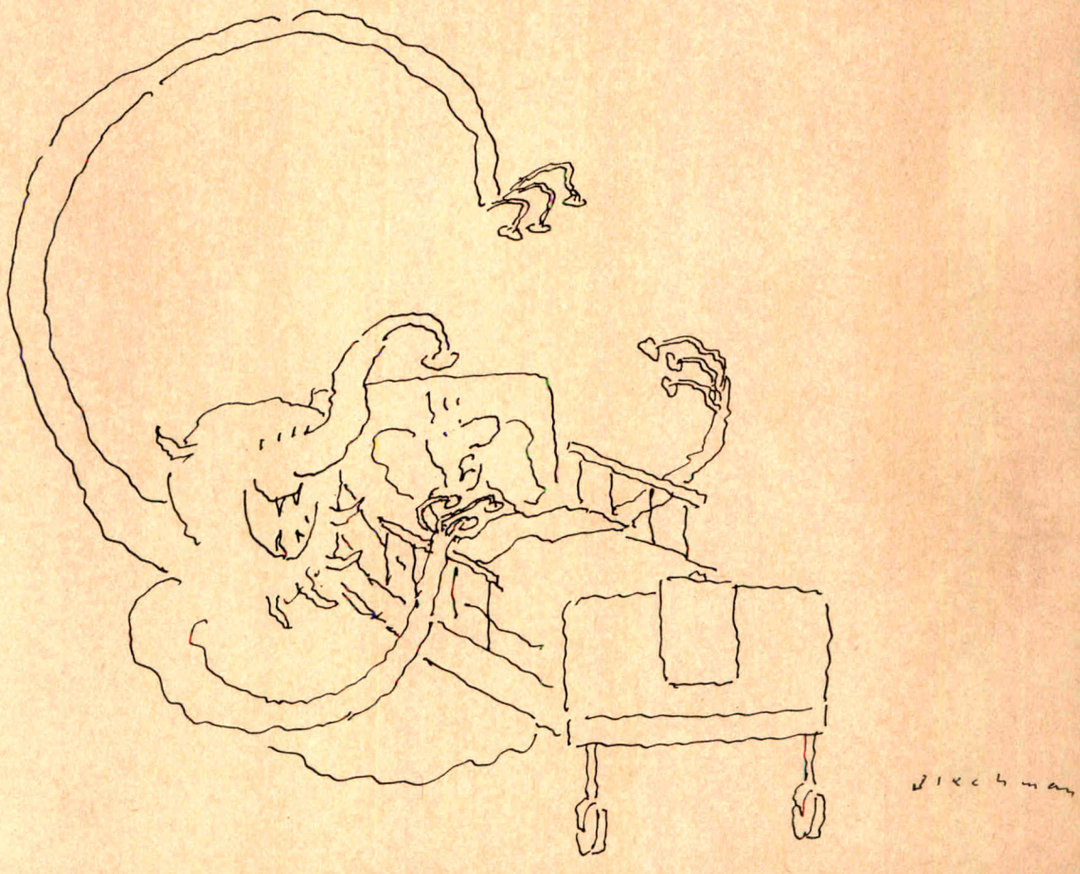

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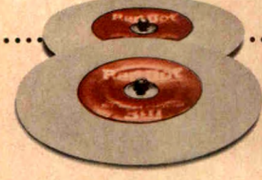

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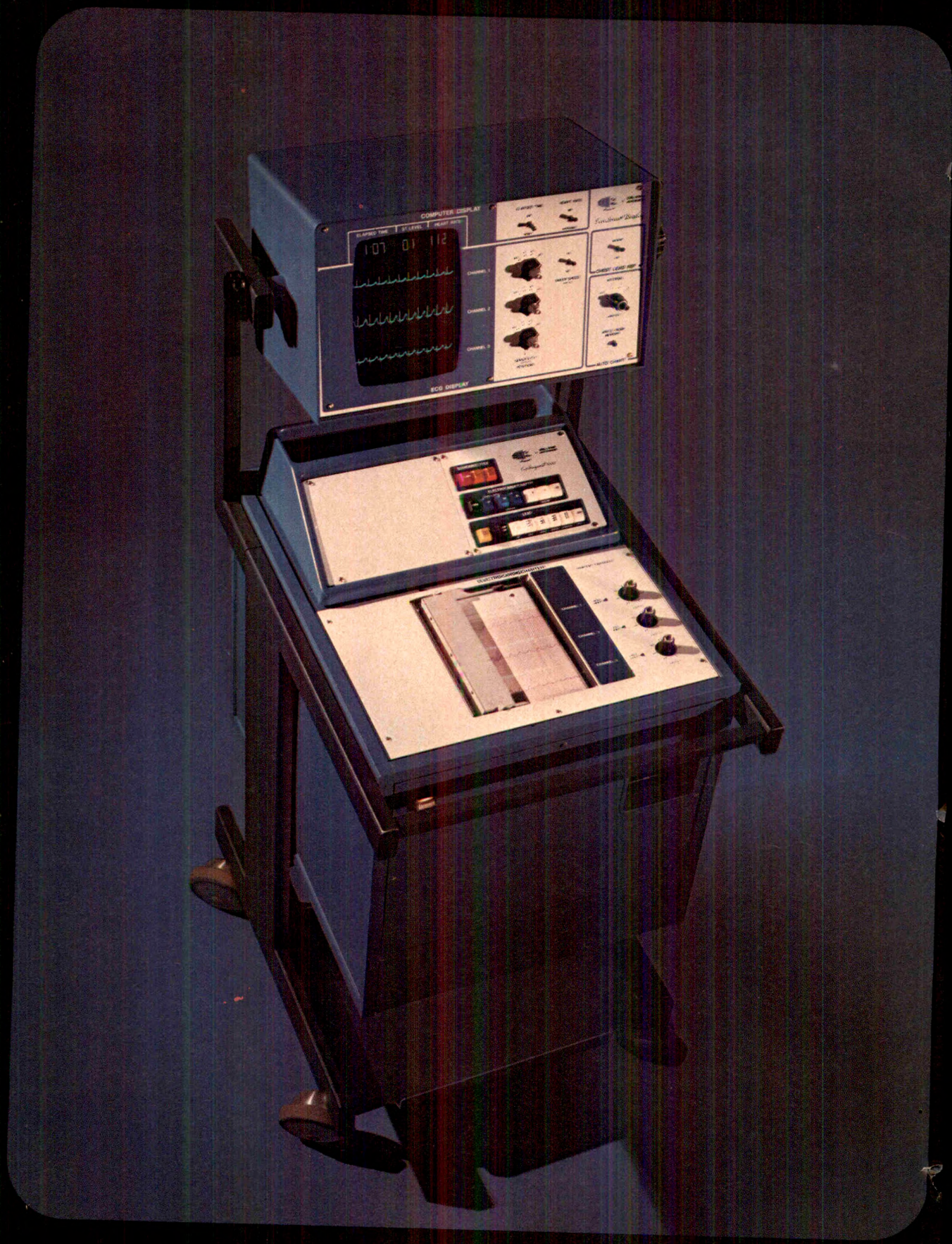

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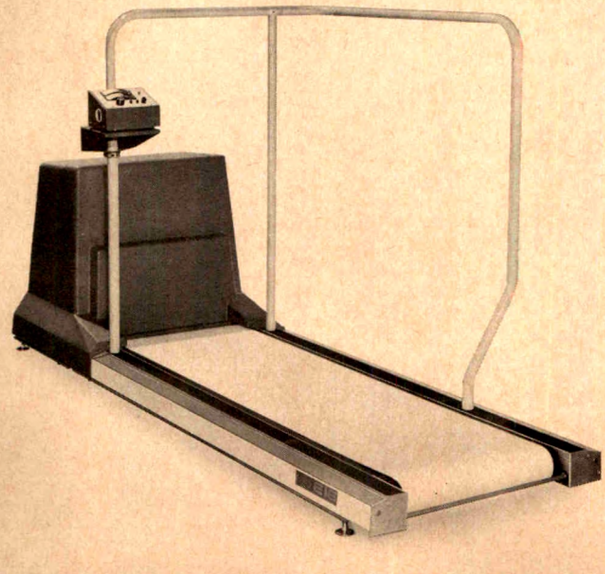

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CLINICAL STUDIES

Thallium-201 Myocardial Perfusion Scintigraphy to Evaluate Patients After Coronary Bypass Surgery

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To determine the utility of thallium-201 stress scintigraphy in assessing the results of coronary bypass surgery, chest pain, stress electrocardiograms and scintigrams were evaluated in 27 patients postoperatively. These findings were compared with coronary angiographic data in which a significant postoperative lesion was defined as 75 percent or more stenosis in a graft, its distal vessel or in an ungrafted native vessel. As an indicator of postoperative coronary lesions, chest pain lacked sensitivity (60 percent) and was nonspecific (20 percent). The stress electrocardiogram had poor sensitivity (60 percent) and good specificity (86 percent) but was not helpful in six patients who had equivocal or suboptimal tests. The scintigram had good sensitivity (77 percent) and was highly specific for the diagnosis of coronary stenosis. It was significantly more specific than chest pain ($P < 0.01$), gave excellent localizing information and added to the accuracy of both conclusive and inconclusive stress tests. In nine patients with preoperative stress scintigrams, comparison of pre- and postoperative studies reflected the effects of bypass surgery on coronary perfusion. Scintigraphy is a useful technique for the noninvasive evaluation of the patient after coronary bypass surgery, and postoperative scintigraphy alone is of great value in documenting surgical results.

From the Cardiovascular Division of the Department of Medicine, Nuclear Medicine Division of the Department of Radiology and the Cardiovascular Research Institute, University of California, San Francisco, California. This work was supported in part by Program Project Grant HL 06285 from the National Heart, Lung, and Blood Institute and Federal Contract HV 52989 under the Myocardial Infarction Program, U. S. Public Health Service, National Institutes of Health, Bethesda, Maryland. Manuscript received November 28, 1977; revised manuscript received March 28, 1978, accepted March 29, 1978.

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Each year in the United States an estimated 50,000 coronary arterial bypass procedures are performed.[1] As a consequence, there is now a large group of patients who have undergone this procedure and will require follow-up evaluation for the presence of myocardial ischemia. Although useful information on such patients is obtained from a history of symptomatic improvement, the resting electrocardiogram and the functional and electrocardiographic response to graded exercise, evaluation of the extent of revascularization and graft patency relies on repeat coronary angiography. Because angiography is costly and time-consuming and subjects the patient to a small but definite risk,[2,3] its use has been limited in the follow-up of patients after bypass surgery.

TABLE I
Clinical Data in 27 Patients After Coronary Bypass Surgery

Case no.	Age (yr) & Sex	Preoperative							Postoperative				
		Tl-201		Stress ECG	Min on Treadmill	Angiography (% Stenosis)			Chest Pain	Tl-201		Stress ECG	Min on Treadmill
		Stress	Rest			LAD	LCx	RCA		Stress	Rest		
1	44M	...	...	...	...	Pat G	Pat NV	Pat NV	Typical	−	...	−	Paced
2	57M	...	...	...	...	Pat G	Pat NV	Pat NV	Typical	−	...	−	Paced
3	51M	+	−	I	4.5	Pat G × 2	Pat G	Pat G	None	−	...	−	9.0
4	50F	+	−	I	2.0	Pat G	Pat G	Pat G	Atypical	−	...	±	6.0
5	33M	...	...	...	...	Pat G × 2	Pat G	Pat NV	Atypical	−	...	−	12.6
6	48M	...	...	...	...	Pat G	Pat G	Pat G	None	−	...	−	11.8
7	69M	...	...	...	...	Pat G × 2	Pat G	Pat G	Atypical	+	+	+	3.1
8	55M	+	−	0	6.0	Pat G	Pat G	Pat G	Typical	−	...	−	6.0
9	52M	...	...	...	...	Pat G	Pat NV	Pat G; 100% G*	Typical	−	...	−	8.3
10	57M	+	−	I	4.0	Pat G	Pat G	Pat NV	Atypical	−	...	−	9.0
11	54M	...	...	...	...	Pat G; 90% NV	Pat G; 90% NV	90% NV	None	−	−	−	8.7
12	47M	...	...	...	...	Pat NV	Pat G; 90% NV	Pat G	Typical	++	+	+	11.1
13	58F	++	+	I	4.0	Pat G; 90% NV	Pat G; 90% NV	Pat G	None	++	+	−	6.0
14	44M	...	...	...	...	80% G; 100% G	Pat NV	Pat NV	None	++	+	+	13.3
15	47M	...	...	...	...	80% NV	100% G	90% G	Typical	+	−	+	6.6
16	59M	...	...	...	...	Pat G; 90% NV	Pat NV	100% G	Typical	+	−	±	4.1
17	52M	...	...	...	...	Pat G	100% G	100% NV	Typical	+	+	Subop	8.0
18	41M	+	+	0	3.0	Pat G; 100% G	90% G	100% G	None	+	+	−	7.2
19	55M	...	...	...	...	100% G	Pat G	100% G	Atypical	+	+	Subop	3.5
20	50M	...	...	...	...	Pat G; 100% G	Pat G × 2	Pat NV	None	+	+	−	7.6
21	65F	...	...	...	...	100% G	100% G	Pat G	Atypical	+	−	+	5.0
22	55F	...	...	...	...	Pat G	100% G	Pat NV	Typical	+	−	+	6.1
23	65M	...	...	...	...	Pat G	100% G	100% G	Typical	+	−	±	3.0
24	56M	...	...	...	...	100% G × 2	100% G	Pat NV	Typical	+	−	±	2.0
25	50M	+	−	I	3.0	100% G	Pat G	Pat G	None	+	−	+	6.0
26	62M	+	−	I	3.0	...	...	...	None	−	−	−	6.0
27	42M	++	−	Eq	3.0	...	...	...	None	+	+	±	5.1

* Review of pre- and postoperative angiograms reveals no significant stenosis in native right coronary artery.
− = no perfusion defect; + = perfusion defect; ++ = new perfusion defect in addition to defect at rest; 0 = no ischemic S-T change.
ECG = electrocardiogram; Eq = equivocal because of baseline S-T abnormalities; G = graft; I = ischemic S-T change; LAD = left anterior descending coronary arterial system; LCx = left circumflex coronary arterial system; Min = minutes; NV = native vessel; Pat = no significant stenosis; RCA = right coronary arterial system; Subop = exercise test suboptimal because less than 85 percent of maximal predicted heart rate was achieved; Tl = thallium.

Thallium-201 stress scintigraphy is a noninvasive method for assessing regional myocardial perfusion and, indirectly, identifying significant coronary stenosis.[4–6] It has been successfully used in evaluating patients with coronary artery disease.[4–6] In this study we examined the value of the method in follow-up studies of patients after bypass surgery. We also compared the results obtained with pre- and postoperative stress scintigraphy with those obtained with postoperative studies alone.

Methods

Patients: The 27 patients studied (Table I) represent all patients who underwent thallium-201 stress scintigraphy at this institution as part of follow-up evaluation after coronary bypass surgery. Nine of these patients (Patients 3, 4, 8, 10, 13, 18 and 25 to 27) had undergone stress scintigraphy preoperatively. Twenty-five (Patients 1 to 25) also underwent postoperative selective coronary angiography. The age of the 23 men and 4 women averaged 52.5 years (range 33 to 69). In 17 patients the postoperative evaluation was undertaken because of recurrent chest pain; 11 of the 17 had typical angina pectoris. Ten patients who were free of chest pain were studied because the patient or his physician desired information regarding graft patency. Two patients were experiencing pain at rest. Four (Patients 8, 15, 16 and 22) were receiving propranolol, and seven (Patients 4, 7, 13, 19, 20, 23 and 27) were receiving digoxin at the time of study. Two patients had a single graft; 9 had double, 12 had triple and 4 had quadruple bypass grafts (average 2.7 grafts per subject). Thirty-two grafts were placed to the left anterior descending coronary artery or diagonal vessels, 23 to the left circumflex or marginal vessels and 17 to the right coronary artery. With the exception of three internal mammary artery grafts to the left anterior descending coronary artery, saphenous veins were used in all instances.

Stress testing: In 25 patients stress perfusion scintigraphy was performed in relation to graded treadmill exercise according to the method of Bruce.[7] A 12 lead electrocardiogram was taken at rest and an intravenous catheter was placed in an antecubital vein to facilitate administration of thallium-201. The blood pressure and CM_5 electrocardiographic lead were monitored during standing, hyperventilation, exercise

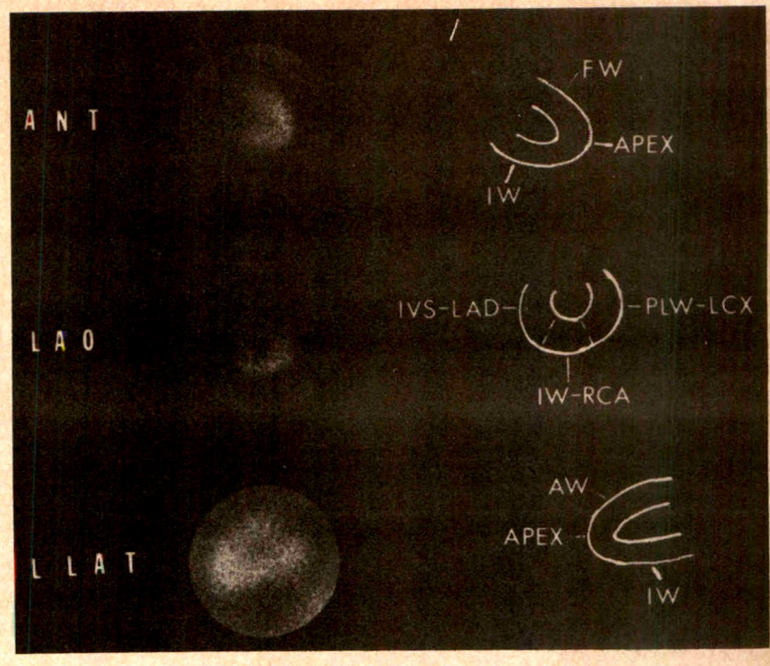

FIGURE 1. Patient 4. Complete revascularization with three patent grafts on angiography. The postoperative thallium-201 stress scintigrams (**left**) show that myocardial perfusion is homogeneous; no defect is seen in any projection. A schematic interpretation of each projection (**right**) demonstrates the method used to localize defects to the distribution of the coronary artery. ANT = anterior; AW = anterior left ventricular wall; FW = free left ventricular wall; IVS = interventricular septum; IW = inferior left ventricular wall; LAD = left anterior descending system distribution; LAO = left anterior oblique projection; LCX = left circumflex coronary system distribution; L LAT = left lateral projection; PLW = posterolateral left ventricular wall; RCA = right coronary arterial distribution.

and a 6 to 8 minute recovery period. The treadmill electrocardiogram was considered abnormal and positive for ischemia if there was 1 mm or greater horizontal or downsloping S-T segment depression below an isoelectric baseline, 0.08 second from the J point, during exercise or in recovery. The treadmill electrocardiogram was called equivocal for the diagnosis of ischemia, regardless of the degree of exercise-induced S-T segment depression, if the baseline S-T segment was depressed greater than 1 mm. Negative treadmill tests in which 85 percent of the maximal predicted heart rate for age was not reached were classified as suboptimal studies.

In two patients (Patients 1 and 2) with pain at rest of apparent cardiac origin, stress perfusion scintigraphy was performed in conjunction with atrial pacing.[8] A no. 7 French bipolar pacing catheter was positioned in the upper right atrium. Pacing was begun at 20 beats/min above the sinus rate and increased by 10 to 15 beats/min at 2 minute intervals until limited by the patient's symptoms or block at the atrioventricular node. Electrocardiographic monitoring and evaluation were performed as during exercise.

Electrocardiograms were interpreted by two independent observers who had no knowledge of the patient's identity, coronary anatomy or scintigraphic findings. There was complete agreement in 96 percent of the studies and minor disagreement in 4 percent; assessment of the latter was determined by consensus with the aid of a third observer.

Perfusion scintigraphy: All scintigrams were obtained with the patient in a fasting state. Thallium-201 was administered in a dose of 1.5 to 2.0 millicuries intravenously at peak stress and, when indicated, at rest (see later). Exercise or pacing was continued for 60 seconds after the administration of thallium. Imaging was begun within 10 minutes of administration of thallium and was generally completed within 30 minutes. Scintigraphy was performed using either a portable (Ohio Nuclear, Solon, Ohio) or stationary (Pho Gamma IV, Searle Radiographics, Inc., Des Plaines, Illinois) 37 phototube camera equipped with a converging collimator and employing a 20 percent window centered at 75 KeV. Hepatic and splenic radioactivity was shielded when significant.

To ensure adequate evaluation of relative myocardial radioactivity, an image was taken to 200,000 counts in the anterior projection and the time noted. Then images in the 45° left anterior oblique and left lateral projections were taken to equal time. Unprocessed images printed on Polaroid® film were obtained for the initial 15 studies. In 12 patients studied thereafter, images were also acquired on a PDP 11/40 computer, and image enhancement was performed by spreading the gray scale between peak cardiac radioactivity (upper threshold) and a mean background level (lower threshold). Although computer processing made the defects in the analog images appear more prominent and occasionally increased the security of interpretation, all defects were identified from the analog image.

Patients with a normal stress scintigram were not restudied. Patients with an abnormal stress scintigram were restudied at rest in all three projections, using the same camera and imaging technique, 1 week after the initial study. After initiation of the repeat studies, it became apparent that a delayed resting image, obtained 4 hours after the stress study, accurately depicted the resting perfusion state.[9] Patients at our institution are now studied with the delayed image technique. Scintigraphy was performed an average of 16.3 (range 2 to 70) months postoperatively. Among 25 patients who underwent postoperative coronary angiography, scintigraphy was performed within 1 month of angiography in 21 patients, and within 4 months in all patients. No patient had a history of an ischemic event between the two tests. The results of preoperative thallium-201 stress scintigraphy were available for comparison with postoperative studies in nine patients.

Stress scintigrams that revealed new or enlarged defects when compared with the image at rest indicated segments of relative hypoperfusion and were considered positive for stress-induced myocardial ischemia. Scintigraphic defects at rest were interpreted as evidence of prior infarction. The postoperative scintigrams were compared with those obtained preoperatively and changes in perfusion noted. Scintigrams were evaluated by two independent observers without

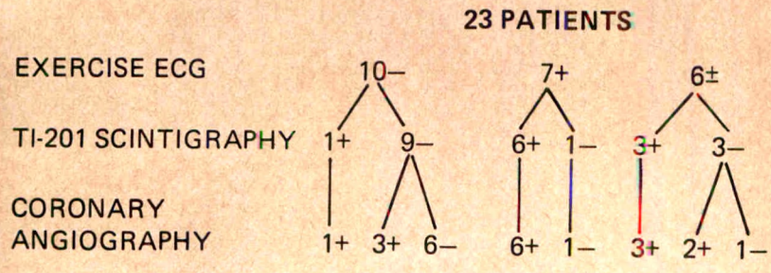

FIGURE 2. Comparison of thallium (Tl)-201 stress scintigraphy and exercise electrocardiography (ECG) in relation to angiographic results. − = exercise or scintigraphic study negative for ischemia or no angiographic evidence of coronary artery disease; + = exercise or scintigraphic study with stress-induced ischemic change or angiographic evidence of coronary artery disease; ± = equivocal or suboptimal study.

knowledge of the patient's identity, coronary anatomy or the results of stress testing. Observer agreement was complete in 92 percent of images. Minor observer disagreement concerning the location or extent of abnormalities occurred in 8 percent of images; the final interpretation was decided by consensus with the aid of a third independent observer.

Scintigraphic defects were localized to regions of coronary perfusion according to the known coronary anatomy. Each scintigraphic projection was divided into three left ventricular segments (Fig. 1). The anterior projection was divided into the anterior or free wall, apex and inferior wall; the left anterior oblique projection into the posterolateral wall, inferior wall and septum; and the left lateral projection into the anterolateral wall, apex and inferior wall. Hypoperfusion in the distribution of the left anterior descending coronary artery was diagnosed if scintigraphic defects involved the septum with or without involvement of the anterolateral wall; hypoperfusion in the distribution of the left circumflex artery was diagnosed if defects involved the posterolateral wall; and hypoperfusion in the distribution of the right coronary artery was diagnosed if defects involved the inferior wall. Because apical abnormalities could result from hypoperfusion in the distribution of any of the three vessels, localization depended on the presence of accompanying scintigraphic abnormalities.

Coronary angiography: Selective coronary angiography with visualization of grafts and the native coronary circulation was performed in multiple projections with the Judkins technique in 25 patients. If a graft could not be demonstrated on selective angiography and if there was no definite evidence of graft closure at the aortic anastomosis, aortic root biplane angiography was performed in the 60° left anterior oblique and the 30° right anterior oblique projections. The degree of coronary and graft stenosis was determined by agreement of two independent observers who were unaware of the results of scintigraphy or stress testing. Narrowing of diameter by 75 percent or more in a graft, the coronary artery distal to the graft or a major coronary artery that had not been grafted was considered significant.

Results

The results from all 27 patients are shown in Table I.

Coronary anatomy: Significant stenosis existed in the native vessel proximal to the site of graft insertion in all but one grafted vessel (in Patient 10); thus, perfusion was dependent on the integrity of the graft. Complete revascularization was thought to be present in Patients 1 to 9, in whom all grafts, distal vessels and major native ungrafted vessels were free of significant stenosis, and in Patient 10, who had an occluded graft to the right coronary artery but no significant stenosis in the native artery. Three patients (Patients 11 to 13) with patency of all grafts had stenosis either distal to a patent graft or in an ungrafted native vessel. Twelve patients (Patients 13 to 25) were found to have stenosis in one or more grafts.

Chest pain: Seventeen of the 25 patients who underwent angiography had chest pain. Nine of these patients had stenosis of either a graft or a native vessel (Patients 12, 15 to 17, 19 and 21 to 24), whereas eight (Patients 1, 2, 4, 5 and 7 to 10) were considered to have complete revascularization. In none of these patients did the history, examination or laboratory evaluation suggest postcardiotomy syndrome. Among the 11 patients with a history of typical angina, 7 (Patients 12, 15 to 17 and 22 to 24) had stenosis in either a graft or a native vessel; however, 4 (Patients 1, 2, 8 and 9) were considered to have complete revascularization. Among eight patients without chest pain who underwent angiography, only two (Patients 3 and 6) had complete revascularization. Overall, chest pain was present in 9 of 15 patients with a significant postoperative coronary abnormality, and thus had a sensitivity rate of 60 percent. Chest pain was absent in only 2 of 10 patients with angiographic evidence of complete revascularization (specificity rate only 20 percent).

Postoperative exercise stress testing: The results of all 23 patients undergoing postoperative graded exercise testing who also had follow-up coronary angiograms are shown in Table I and Figure 2. In this group, six tests (in Patients 4, 16, 17, 19, 23 and 24) were inconclusive because of suboptimal stress in two patients, baseline S-T segment changes in three patients and rate-related left bundle branch block in one patient. Five of these six patients (all but Patient 4) had significant stenosis in either a graft or a native vessel. Among the remaining 17 patients, angiographic evidence of significant narrowing in either a graft or a native vessel was seen in 6 of the 7 patients with a positive stress test (Patients 12, 14, 15, 21, 22 and 25), but also in 4 of the 10 with a negative stress test (Patients 11, 13, 18 and 20). When the equivocal tests were excluded, 6 of 10 patients with significant postoperative coronary arterial abnormalities had a positive stress electrocardiogram (sensitivity rate 60 percent), and 6 of 7 patients with angiographic evidence of complete revascularization had a negative stress electrocardiogram (specificity rate 86 percent).

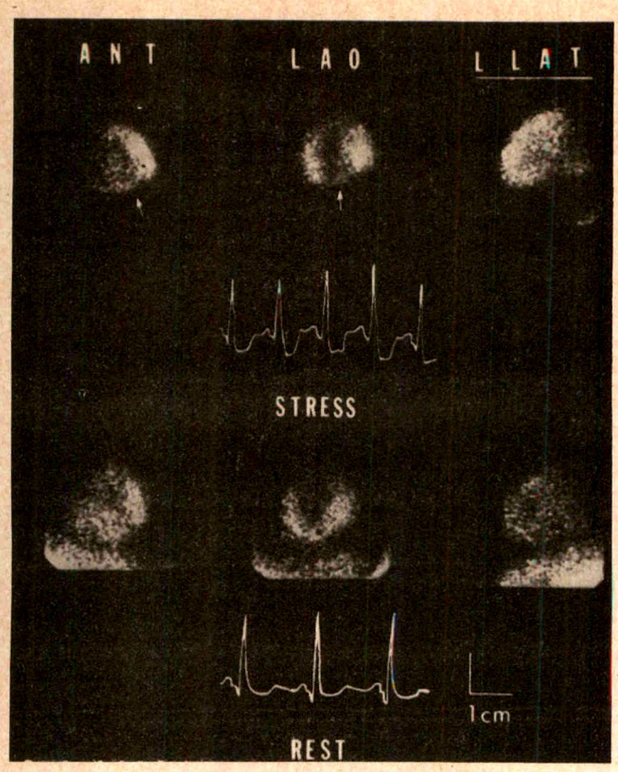

FIGURE 3. Patient 15. Stenosis of graft to the right coronary artery. Thallium-201 scintigrams and electrocardiogram during stress (**above**) and at rest (**below**). During stress, a defect involving the inferior wall is best seen in the left anterior oblique projection (**arrows**). At rest, the images are normal. The scintigraphic study was positive for inferior wall ischemia. Angiography revealed stenosis of grafts to the left circumflex and right coronary arteries and in the ungrafted native left anterior descending coronary artery. The stress electrocardiogram was positive for ischemia. Abbreviations as in Figure 1.

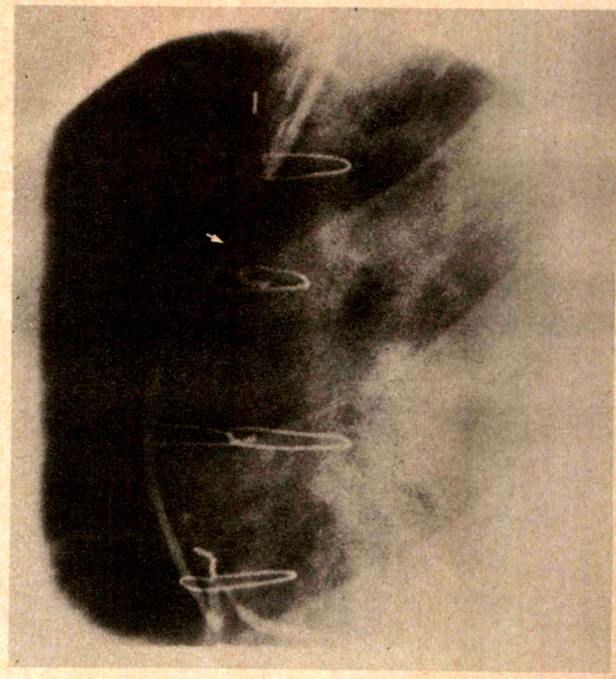

FIGURE 4. Patient 15. Selective visualization of graft to the right coronary artery. Note the high grade proximal stenosis in the graft (**arrow**). Stress scintigraphy revealed a correlative inferior wall defect.

Patients with complete revascularization exercised for a slightly longer time (8.2 versus 7.0 minutes) than those with stenosis of a graft or a native vessel. However, the difference was not significant and could not reliably predict the extent of revascularization in an individual patient.

Two patients (Patients 1 and 2) with chest pain at rest underwent atrial pacing stress. Both had negative S-T responses for ischemia and complete revascularization as assessed with angiography.

Postoperative stress scintigrams: In patients undergoing postoperative coronary angiography, thallium-201 scintigraphy was performed during atrial pacing in 2 patients (Patients 1 and 2) and in association with treadmill testing in 23 patients (Patients 3 to 25). The results are shown in Table I and Figure 2. Overall, results of stress scintigraphy were negative in 15 patierts. In 10 patients (Patients 1 to 6 and 8 to 11), no scintigraphic defect was seen, and in 5 (Patients 7 and 17 to 20), the defect seen during stress was unchanged from the that observed in the study at rest. Two patients (Patients 17 and 19) had a suboptimal stress test, and both had graft stenosis on angiography. Of the patients with a negative scintigram during optimal stress testing, 10 of 13 (77 percent) were considered to have complete revascularization. The data from one such patient are shown in Figure 1. Of the three patients with a negative scintigram and vessel stenosis, two (Patients 11 and 18) had stenosis in the distribution of all three coronary vessels. Patient 18 also had a large defect at rest. Neither patient had well developed collateral vessels on angiography. The other patient with a negative stress scintigram (Patient 20) had a fixed defect during rest and exercise in a region supplied by an occluded graft. The distal native vessel received considerable collateral flow from an adjacent successfully grafted vessel.

All 10 patients with a positive stress scintigram (Patients 12 to 16 and 21 to 25) had significant angiographic lesions in vessels perfusing the region of scintigraphic abnormality. Eight patients had stenosis of one or more grafts. An example of a positive scintigram with an inferior defect is shown in Figure 3. On angiography, stenosis of the right coronary bypass graft was demonstrated (Fig. 4). An example of a positive scintigram with anterior and septal defects is shown in Figure 5. Two patients with a positive scintigram had fully patent grafts, but their angiograms revealed stenosis in an ungrafted native vessel (Patient 12) or stenosis distal to graft insertion (Patient 13). Ten of 13 optimally stressed patients with significant postoperative coronary abnormalities had a positive scintigram (sensitivity rate 77 percent), and all 10 patients with angiographic evidence of complete revascularization had a negative scintigram (specificity rate 100 percent).

TABLE II

Accuracy of Stress Scintigraphy in Localizing Hypoperfusion in Patients After Coronary Bypass Surgery

Vessel	Vessels Studied (no.)	Coronary Stenosis on Angiography	Tl-201 Stress Defect
LAD	25 (23)	11	6
LCx	25 (20)	10	5
RCA	25 (17)	7	3
Total	75 (60)	28	14

Sensitivity to coronary abnormalities = true positive scintigraphic segments/true positive + false negative scintigraphic segments = 14/28 = 50%.

Specificity to coronary abnormalities = true negative scintigraphic segments/true negative + false positive scintigraphic segments = 47/47 = 100%.

Figures in parentheses indicate subjects with at least one bypass graft to the coronary system noted.

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

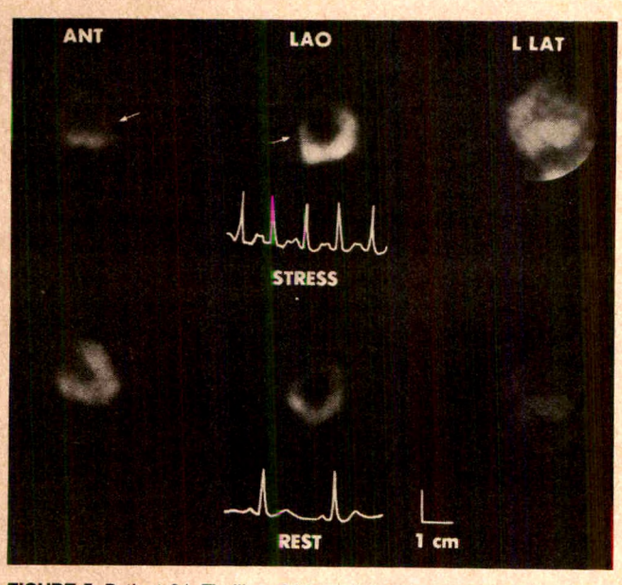

FIGURE 5. Patient 21. Thallium-201 scintigrams and electrocardiogram during stress (**above**) and at rest (**below**). Large defects involving the anterior wall septum during exercise (**arrows**) were not present at rest and suggest stenosis of the graft to the left anterior descending coronary artery. Angiography revealed stenosis of grafts to both this artery and the left circumflex coronary artery. The full stress electrocardiogram was positive for ischemia. Abbreviations as in Figure 1.

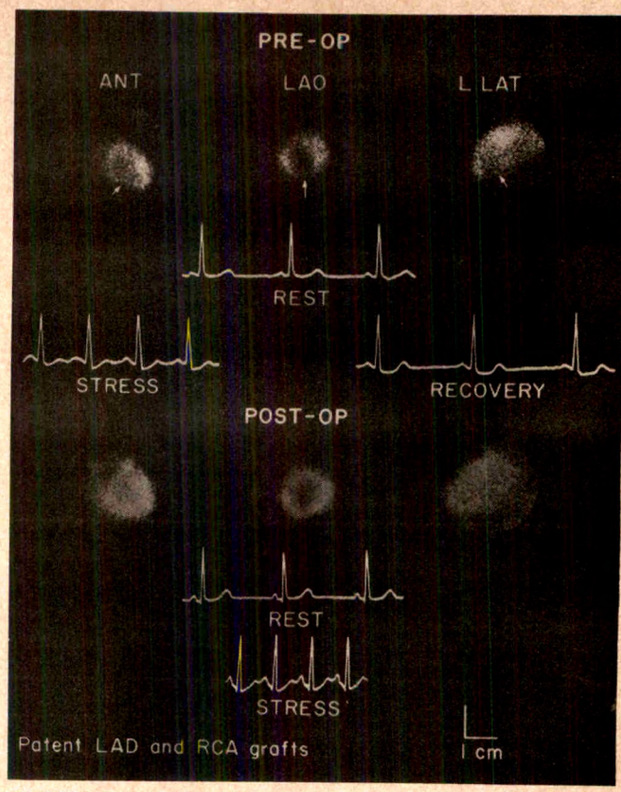

FIGURE 6. Patient 26. Pre- and postoperative evaluation—good result. Thallium-201 stress scintigrams and electrocardiograms obtained before (**above**) and after (**below**) coronary bypass surgery. The preoperative study revealed an inferior wall perfusion abnormality seen best in the left anterior oblique projection (**arrow**) as well as an ischemic electrocardiographic response at a low level of exercise stress. After placement of a graft to the right coronary artery, the patient became symptom-free and demonstrated normal scintigraphic and electrocardiographic findings at much increased exercise stress. Angiography was not performed; however, the scintigraphic findings document reperfusion. POST-OP = postoperative; PRE-OP = preoperative; other abbreviations as in Figure 1.

Stress scintigraphic localization of ischemic regions through the distribution of the major vessels is outlined in Table II. The stress scintigram in the vascular distribution of the left anterior descending coronary artery (Fig. 5) was positive in 6 of the 25 patients (Patients 13, 14, 16, 21, 24 and 25). All had significant narrowing of the graft or of the distal native vessel. The stress scintigram of five patients was positive, with defects in the distribution of the left circumflex coronary artery. Three of the five (Patients 22 to 24) had significant graft stenosis; the two others (Patients 12 and 13) had patent grafts but significant stenosis in a major ungrafted branch of the circumflex system. Three patients (Patients 15, 16 and 23) had a positive stress scintigram in the distribution of right coronary artery (Fig. 3). All three had stenosis of the graft to the right coronary artery.

The perfusion pattern involving the distribution of 75 vessels in 25 patients was assessed. In all cases, a positive scintigram correctly localized stenosis to the distribution of the appropriate vessel. When all vessels with stenosis were considered, 14 of 28 (50 percent) were identified with stress scintigraphy. Of the 14 stenotic vessels not identified, 5 were distributed to segments with defects at rest that did not change during exercise. Thallium-201 imaging thus localized 19 of 28 vessels (68 percent) with significant stenosis. Stress scintigraphy was totally specific and in no instance did it demonstrate hypoperfusion of the segment unless there was a corresponding stenosis in the vascular supply.

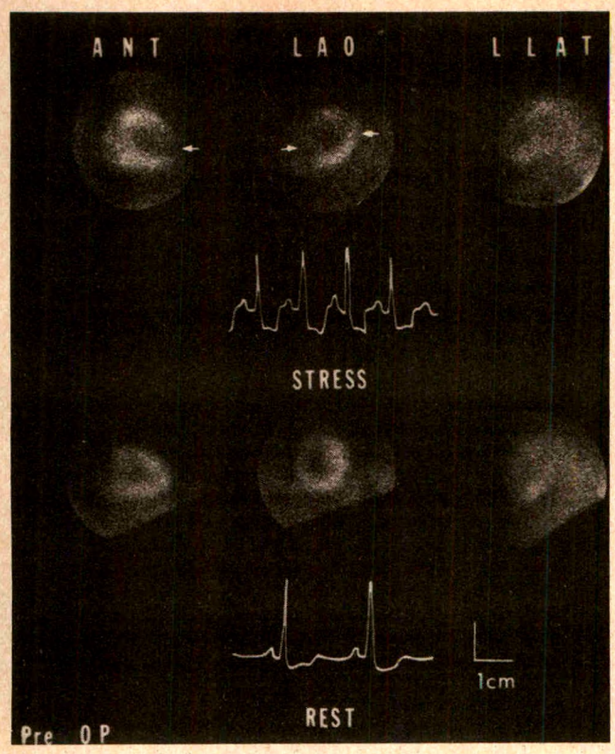

FIGURE 7. Patient 13. Preoperative evaluation. Thallium-201 scintigrams and electrocardiograms during stress (**above**) and at rest (**below**) from a patient with a prior anteroseptal infarction. Defects involving the anterior wall, septum and posterolateral wall are seen during stress (**arrows**). Angiography revealed triple vessel disease. The stress electrocardiogram was judged equivocal because of baseline S-T segment depression. Pre OP = preoperative; other abbreviations as in Figure 1.

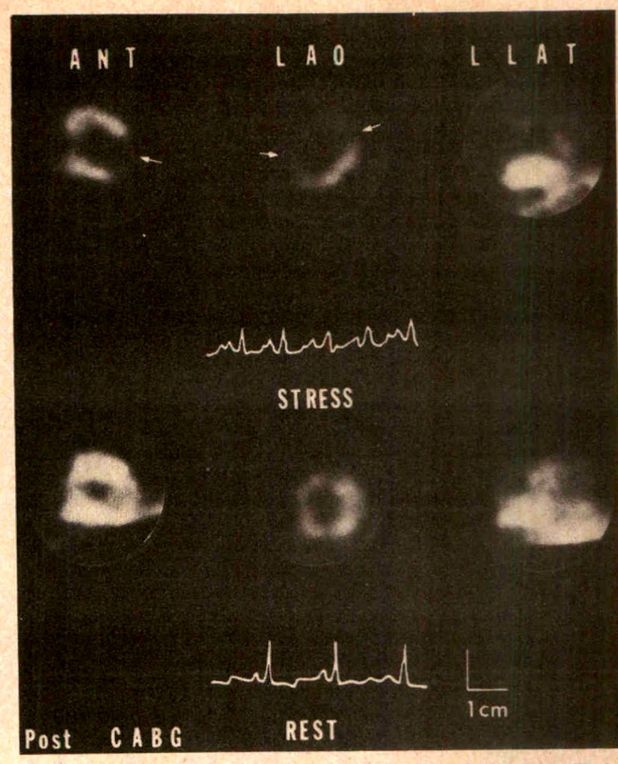

FIGURE 8. Patient 13. Postoperative evaluation—poor result. Thallium-201 scintigrams and electrocardiogram during stress (**above**) and at rest (**below**) after coronary bypass surgery (CABG). The patient was asymptomatic and had a normal exercise test postoperatively. However, scintigraphy suggested continued stress-induced ischemia and angiography revealed 90 percent stenosis of a large ungrafted vessel in the left circumflex system as well as stenosis of the left anterior descending coronary artery distal to one of the three patent grafts. Abbreviations as in Figure 1.

Comparison of pre- and postoperative scintigrams: Nine patients (Patients 3, 4, 8, 10, 13, 18 and 25 to 27) were evaluated with stress scintigraphy both before and after operation. Six patients (Patients 3, 4, 8, 10, 26 and 27) who exercised to the same or a higher level than that attained preoperatively had scintigraphic evidence of improved perfusion. Four of these patients, three with persistent pain, were shown to have complete revascularization. The other two (Patients 26 and 27) did not have a postoperative angiogram. The data from the former patient are shown in Figure 6. In three patients (Patients 13, 18 and 25), all free of chest pain, the postoperative stress scintigram was unchanged from the preoperative study. In all three patients, significant stenosis was found on angiography. The pre- and postoperative scintigrams of Patient 13 are shown in Figures 7 and 8.

Because the postoperative scintigram successfully predicted revascularization in the seven patients who underwent repeat angiography, preoperative scintigraphy did not contribute to the predictive accuracy of the method.

Stress scintigraphy compared with chest pain and stress electrocardiography: The sensitivity of postoperative chest pain (60 percent), abnormal stress electrocardiogram (60 percent) and stress scintigraphic abnormalities (77 percent) for the presence of postoperative coronary abnormalities showed no significant differences, and each indicator was moderately successful in identifying patients with incomplete revascularization. However, the scintigram was 100 percent specific for postoperative coronary abnormalities and was more specific than chest pain ($P < 0.01$) in identifying such abnormalities. Although the specificity of the stress electrocardiogram was not significantly different from that of the scintigram, the latter study occasionally identified patients with false positive (Patient 7) or false negative (Patient 13) stress tests. An example of a false negative electrocardiogram and correctly positive scintigram in a patient with stenosis of the left anterior descending and left circumflex coronary arteries is shown in Figure 8.

Exercise testing was inconclusive in six patients (Patients 4, 16, 17, 19, 23 and 24). Scintigraphy was positive in three of these patients (Patients 16, 23 and

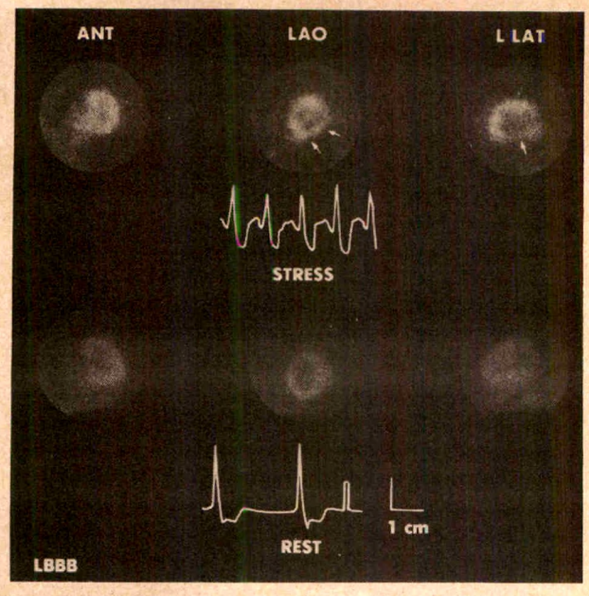

FIGURE 9. Double graft closure—equivocal electrocardiogram. Patient 23. Thallium-201 scintigrams and electrocardiogram during stress (**above**) and at rest (**below**). Defects involving the posterolateral and inferior walls during exercise (**arrows**) are not present at rest. These findings are consistent with exercise-induced ischemia in the distribution of the left circumflex and right coronary arteries. Angiography revealed stenosis of grafts to both these arteries. The electrocardiogram was considered equivocal because of resting electrocardiographic changes in association with left bundle branch block (LBBB). Abbreviations as in Figure 1.

24), all of whom had significant stenosis on angiography. The data from Patient 23 are shown in Figure 9. The results of scintigraphy were negative in three patients, including one (Patient 4) who had complete revascularization. The two patients with a negative scintigram and stenosis on angiography (Patients 17 and 19) had a suboptimal stress test.

Prior infarction: Among the 27 patients included in the study, 9 (Patients 7, 12 to 14, 17 to 20 and 27) had an abnormal scintigram at rest. Seven of these subjects had Q waves in the electrocardiogram in the distribution corresponding to the perfusion defect. An additional defect was seen on stress scintigraphy in three of these patients, each with a related graft or native vessel stenosis (Patients 12 to 14). Of the six patients with a negative stress scintigram who had a fixed defect, three (Patients 17 to 19) had stenosis of a vessel in addition to the vessel supplying the segment of myocardium that manifested the defect at rest.

Discussion

Thallium-201 is a monovalent cation whose myocardial uptake in viable tissue is proportional to regional coronary blood flow. Of the radionuclides currently available to evaluate noninvasively myocardial perfusion, thallium-201 appears to have the best physical properties for obtaining high resolution perfusion images.[10] Perfusion defects during thallium-201 imaging appear to correlate well with coronary stenosis.[4–6] This study was designed to assess the use of thallium-201 stress scintigraphy in the follow-up evaluation of patients after coronary bypass surgery and to correlate the scintigraphic findings with coronary anatomy.

Positive stress scintigram: Thallium-201 stress scintigrams were positive in 10 of 25 patients who underwent repeat angiography. All 10 had 75 percent or greater narrowing of at least one vessel. Stenosis was found in the grafts of eight of these patients and in a site distal to the graft insertion or in an ungrafted vessel in the other two patients. Had angiographic evaluation been confined to examination of the grafts, the scintigrams of the latter two patients might have been considered examples of false positive studies. Their presence in this series helps to underscore the complexity of the vascular supply in the patient after coronary bypass, and to point out conditions, other than graft stenosis, that could lead to hypoperfusion and result in poor postoperative results.

Negative stress scintigram: Thallium-201 stress scintigrams were negative in 15 patients who underwent repeat angiography. Ten of these patients were considered to have complete revascularization. Two patients with graft stenosis had negative thallium-201 scintigrams during suboptimal stress testing. McLaughlin et al.[11] have shown that the ability of stress scintigraphy to identify critical stenosis increases with the level of exercise, and it is possible that these patients did not have perfusion defects because of insufficient stress. In patients with optimal stress, 10 of 13 (77 percent) who had a negative scintigram were considered to have complete revascularization. Combining sensitivity and specificity, the overall rate of scintigraphic accuracy was 85 percent, a level similar to that achieved in patients with coronary artery disease who had not undergone bypass surgery.[4–6] Because the accuracy of the scintigrams was assessed by comparing them with the angiographic data, three patients appeared to have a false negative scintigram. An alternative possibility is that hypoperfusion did not develop in these patients, despite the presence of what was considered significant stenosis. Flow to a segment of myocardium that is apparently perfused by a stenotic graft or native vessel may not depend exclusively on this single coronary vessel. Collateral flow, possibly originating from a successfully grafted adjacent vessel, may be sufficiently great to protect against stress-induced hypoperfusion. Significant collateral flow to a region served by a stenotic graft was noted in one of our patients.

Other possible reasons for a negative scintigram in patients with coronary stenosis were sought. In two patients (Patients 18 and 20), a large defect at rest representing prior infarction probably decreased our ability to recognize stress-induced hypoperfusion. Because scintigraphic defects depend on relative hypoperfusion of a segment of myocardium, a region may be hypoperfused during stress but still have greater perfusion than in an infarcted region and thus not be recognized. In two patients with triple vessel disease it is possible that stress-induced hypoperfusion developed

in a homogeneous pattern so that localized relative perfusion defects were not seen.[12]

Although many of our patients were receiving propranolol or digoxin, or both (drugs that could affect the distribution of thallium-201), our good results, as well as those reported previously in patients evaluated for the presence of coronary disease,[6] suggest that these drugs have a minimal effect on the scintigram.

Sensitivity of a positive stress scintigram: Although a positive thallium-201 stress scintigram accurately localized the presence of a stenotic vessel in each case, it did not identify all stenotic vessels. In our series, 50 percent of all stenotic grafts or native vessels, or both, were identified with stress scintigraphy. When defects seen in the resting study were combined with those elicited by stress, 69 percent of stenotic vessels were identified. This lack of overall sensitivity in relating stenosis to perfusion may again possibly be due in part to the effects of collateral vessels. In addition, in several of the patients with multivessel disease, a positive scintigram successfully localized perfusion defects to some but not all of the involved vessels. Because the test detects relative perfusion it is probable that patients with multiple areas of hypoperfusion manifest defects only in the most severely affected regions.

Comparison with other radionuclide studies: Perfusion defects were often subtle (Fig. 3 and 9), and considerable experience is necessary to identify accurately such abnormalities. In our study all scintigraphic defects were identified from the analog images by blinded observers. As suggested by Berger et al.,[13] computer enhancement of images may facilitate interpretation and further increase the diagnostic yield of the procedure.

Zaret et al.[14] compared pre- and postbypass potassium-43 scintigrams to evaluate graft patency and found the method specific but far less sensitive than our method. Their patients with a normal or improved scintigram had at least one patent graft, whereas those whose scintigram was worse or unchanged after operation had all grafts occluded. Lurie et al.[15] showed improvement in the perfusion pattern of 15 patients studied before and after bypass surgery with rubidium-81 stress scintigraphy; however, they did not obtain angiographic confirmation of the surgical results.

Postoperative scintigram as a predictor of revascularization and graft patency: Recent reports have suggested that comparison of pre- and postoperative thallium-201 stress scintigrams can reliably predict graft patency,[16–18] and Ritchie et al.[18] concluded that the presence of an exercise defect in the postoperative study was associated with lowered graft patency rates. Our results confirm that postoperative imaging alone can be used to predict the extent of revascularization and graft patency and that accurate postoperative evaluation is possible in bypass patients who have not been evaluated preoperatively.

In our patients who underwent scintigraphy both pre- and postoperatively, evidence of improved perfusion was seen in patients with successful revascularization. These results are consistent with observations in previous studies[14–18] in which scintigraphic improvement was associated with graft patency and scintigraphic deterioration or lack of scintigraphic change was consistent with graft closure or incomplete revascularization.

Comparison with patient history, exercise capacity and electrocardiographic response to exercise: Although these clinical findings are helpful in the evaluation and management of patients after bypass surgery, they are relatively poor indicators of revascularization and graft patency. In our patients chest pain was a particularly unreliable indicator of the results of surgery and could not discriminate between patients with recurrent vascular stenosis and those with complete revascularization. Although relief of chest pain has been shown to correlate with graft patency,[19,20] the interpretation of symptom relief is complicated by additional factors, including the placebo effect of surgery, perioperative infarction and possibly surgical denervation.[21–23] In the reports of both Sheldon[24] and Kouchoukos[20] and their co-workers, a significant number of patients with graft closure experienced relief of chest pain. The poor discriminating quality of chest pain, even when described as typical angina, in this group of patients differs considerably from the experience in patients not operated on whose angina is reliably correlated with coronary artery disease.[25]

Although improved exercise tolerance has been associated with revascularization,[26,27] individual variation is great and prediction of graft patency is hazardous, particularly when a preoperative test is not available for comparison.[28] In our patients the slight trend toward greater exercise tolerance in patients with complete revascularization was a poor indicator of the status of coronary anatomy in an individual patient.

When thallium-201 stress scintigraphy was compared with stress electrocardiography, scintigraphy appeared to be of greatest value in patients with inconclusive electrocardiograms. Scintigraphy also added to the diagnostic accuracy of stress testing by identifying occasional patients with false positive and false negative electrocardiograms (Fig. 2). Similar results using stress scintigraphy have been reported in the evaluation of patients without bypass grafts.[4–6,12] Additionally, the scintigram offered localizing information that could be quite useful in the evaluation of coronary stenosis after bypass graft surgery.

Possible limitations of study: We monitored only a single CM_5 electrocardiographic lead. The use of multiple leads during stress testing would probably result in increased sensitivity of the stress test to ischemic changes; however, it is probable that the number of false positive results would also increase, leading to a decrease in specificity. Use of multiple leads would probably not resolve the equivocal tests.

The patients in this study constitute a selected group and do not represent the general group of patients undergoing coronary bypass surgery. Almost two thirds of our patients were studied because of recurrent chest pain. A less selected study population would probably result in a smaller incidence of graft occlusion and a

somewhat different rate of scintigraphic accuracy. However, our patients do appear to be representative of patients who require follow-up evaluation postoperatively for clinical indications.

Implications: The effectiveness of thallium-201 myocardial perfusion scintigraphy in patients after coronary bypass surgery appears to be similar to that in patients without such surgery. Factors influencing image sensitivity and specificity also appear to be similar in the two groups. Thallium-201 scintigraphy seems to be an important noninvasive method for assessing myocardial perfusion after bypass surgery. Although comparison of pre- and postoperative studies can be used to document the effects of surgery, postoperative scintigraphy alone can sensitively and specifically detect and localize significant stenosis in grafts or native vessels. The method should serve as a useful noninvasive technique for the future evaluation of the postcoronary bypass patient.

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References

1. **Mundth ED, Austen WG:** Surgical measures for coronary heart disease. N Engl J Med 293:13–19, 75–80, 124–130, 1975
2. **Bourassa MG, Noble J:** Complication rate of coronary arteriography. Circulation 53:106–114, 1976
3. **Shah A, Gnoj J, Fisher VJ:** Complications of selective coronary arteriography by the Judkins technique and their prevention. Am Heart J 90:353–359, 1975
4. **Bailey IK, Griffith LSC, Rouleau G, et al:** Thallium-201 myocardial perfusion imaging at rest and during exercise. Circulation 55: 79–87, 1977
5. **Ritchie JL, Zaret BL, Strauss HW, et al:** Myocardial imaging with thallium-201 at rest and exercise—a multicenter study: coronary angiographic and electrocardiographic correlation (abstr). Am J Cardiol 39:321, 1977
6. **Botvinick EH, Taradash MR, Shames DM, et al:** Thallium-201 myocardial perfusion scintigraphy for the clinical clarification of normal, abnormal and equivocal electrocardiographic stress tests. Am J Cardiol 41:43–51, 1978
7. **Bruce RA:** Exercise testing of patients with coronary heart disease: principles and normal standards for evaluation. Ann Clin Res 3: 323–332, 1971
8. **Botvinick EH, Shames DA, Ratshin RA, et al:** The physiologic assessment of critical coronary stenosis by relative myocardial perfusion imaging with atrial pacing (abstr). Am J Cardiol 37:122, 1976
9. **Pohost GM, Zir LM, Moore RH, et al:** Differentiation of transiently ischemic from infarcted myocardium by serial imaging after a single dose of thallium-201. Circulation 55:294–302, 1977
10. **Strauss HW, Harrison K, Langan JK, et al:** Thallium-201 for myocardial imaging. Relation of thallium-201 to regional myocardial perfusion. Circulation 51:641–645, 1975
11. **McLaughlin PR, Martin RP, Doherty P, et al:** Reproducibility of thallium-201 myocardial imaging. Circulation 55:497–503, 1977
12. **Botvinick EH, Shames DH, Gershengorn KM, et al:** Myocardial stress perfusion scintigraphy with rubidium-81 versus stress electrocardiography. Am J Cardiol 39:364–371, 1977
13. **Berger HJ, Gottschalk A, Zaret BL:** Dual radionuclide study of acute myocardial infarction. Ann Intern Med 88:145–154, 1978
14. **Zaret BL, Martin ND, McGowan RL, et al:** Rest and exercise potassium-43 myocardial perfusion imaging for the noninvasive evaluation of aortocoronary bypass surgery. Circulation 49: 688–695, 1974
15. **Lurie AJ, Salel AF, Berman DS, et al:** Determination of improved myocardial perfusion after aortocoronary bypass surgery by exercise rubidium-81 scintigraphy (abstr). Circulation 52:Suppl II: II-141, 1975
16. **Ormond J, Platt M, Mills L, et al:** Thallium-201 scintigraphy and exercise testing in evaluating patients prior to and after coronary bypass surgery (abstr). Circulation 55, 56:Suppl III:III-131, 1971
17. **Sbarbaro JA, Harischandra K, Cantez S, et al:** Tl-201 imaging in the assessment of coronary artery bypass graft (CABG) patency (abstr). Circulation 55, 56:Suppl III:III-231, 1977
18. **Ritchie JL, Narahara KA, Trobaugh GB, et al:** Thallium-201 myocardial imaging before and after coronary revascularization: assessment of regional myocardial blood flow and graft patency. Circulation 56:830–836, 1977
19. **Alderman EL, Matloff HJ, Wexler L, et al:** Results of direct coronary artery surgery for the treatment of angina pectoris. N Engl J Med 288:535–539, 1973
20. **Kouchoukos NT, Kirklin JW, Oberman A:** An appraisal of coronary bypass grafting. Circulation 50:11–16, 1974
21. **Cobb LA, Thomas GI, Dillard DH, et al:** An evaluation of internal mammary ligation by a double blind technic. N Engl J Med 260: 115–118, 1959
22. **Dimond EG, Kittle CG, Crockett JE:** Comparison of internal mammary artery ligation and sham operation for angina pectoris. Am J Cardiol 5:483–486, 1960
23. **Ross RS:** Ischemic heart disease: an overview. Am J Cardiol 36:496–505, 1975
24. **Sheldon WC, Rincon G, Effler DB, et al:** Vein graft surgery for coronary artery disease: survival and angiographic results in 1,000 patients. Circulation 48:Suppl III:III-184–III-189, 1973
25. **Humphries JO, Kuller L, Ross RS, et al:** Natural history of ischemic heart disease in relation to arteriographic findings. Circulation 49:489–497, 1974
26. **Merrill AJ, Thomas C, Schechter E, et al:** Coronary bypass surgery: value of maximal exercise testing in assessment of results. Circulation 51, 52:Suppl I:I-173–I-177, 1975
27. **Lapin ES, Murray JA, Bruce RA, et al:** Changes in maximal exercise performance in the evaluation of saphenous vein bypass surgery. Circulation 47:1164–1173, 1973
28. **McConahay DR, Valdes M, McCallister BD, et al:** Accuracy of treadmill testing in assessment of direct myocardial revascularization. Circulation 56:548–552, 1977

Serial Myocardial Scintigraphy After a Single Dose of Thallium-201 in Men After Acute Myocardial Infarction

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Serial myocardial scintigraphy after a single dose of thallium-201 in the period immediately after myocardial infarction may demonstrate redistribution of thallium-201 into perfusion defects that were evident in the initial scan. This study tested the hypothesis that evaluation of this redistribution, available within hours of infarction, could provide a more accurate estimate of the eventual perfusion defect than a single thallium-201 image obtained immediately after infarction. The study group comprised 14 patients with a diagnosis on admission of probable acute myocardial infarction. The patients received thallium-201 a mean of 1.3 hours after admission to the coronary care unit. Imaging began 10 minutes after the thallium injection and was repeated 4 to 8 hours later.

Eight patients with acute myocardial infarction had a definite reduction in one or more perfusion defects on serial scintigraphy, possibly indicating reperfusion of transiently ischemic zones. Two patients with acute infarction had an increase in perfusion defects in a second study performed 6 hours after the initial scintigram. In the interval between scans, one patient had a cardiac arrest with clinical evidence of infarct extension after successful resuscitation; the other sustained a lateral extension of the infarct. One patient with acute aortic dissection had normal scans on both studies. All three patients with unstable angina had an abnormal initial scan; on repeat scan, the thallium-201 defect was unchanged in one patient, increased in one and decreased in the third. In the patients with myocardial infarction, repeat thallium-201 scans corresponded more nearly than the initial scans to the extent of technetium-99m stannous pyrophosphate uptake by the heart.

These data suggest that serial myocardial imaging with thallium-201 immediately after myocardial infarction can overcome some of the limitations of a single thallium-201 scintigram and may be useful in delineating ischemic from infarcted myocardium in the postinfarction period.

Techniques for evaluating cardiac performance utilizing radionuclides have been developed and improved in the last few years. Among these techniques are means for assessing myocardial perfusion. Radioactive monovalent cations and radionuclide-labeled microspheres have been the chief agents utilized.[1–3] Of the monovalent cations, thallium-201 has the most desirable radiochemical qualities for gamma camera imaging,[4,5] with a relatively long half-life (73.5 hours) and a satisfactory emission spectrum for collimation and imaging. Myocardial concentration of thallium-201 depends on blood flow[2] and on the integrity of the sarcolemma and its sodium-potassium adenosine triphosphatase [(Na^+-K^+)-ATPase].[6] Recent studies have suggested that thallium-201 scintigraphy is of substantial value in evaluating patients with stable angina pectoris[7] and in detecting acute myocardial infarction.[8] Thallium-201 perfusion defects noted after an acute myocardial infarction have been correlated with infarct size estimated at postmortem examination[9] and

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with the positive scintigraphic image of damaged myocardium detected with agents such as technetium-99m stannous pyrophosphate.[10,11] The role of thallium-201 scintigraphy in assessing patients with acute myocardial infarction is less clear than in patients with stable angina pectoris because scintigraphic defects in the former represent old infarctions as well as new areas of infarction and, possibly, areas of transient ischemia.[8]

Pohost et al.[12] demonstrated that the size of a perfusion defect produced by transient coronary occlusion in dogs or by exercise-induced ischemia in patients with stable angina pectoris will decrease when imaging is performed serially 15 minutes and 4 to 6 hours after a single intravenous dose of thallium-201. They concluded that the change in the image reflects redistribution of thallium-201 into transiently ischemic myocardium and that serial imaging in this manner differentiates infarcted from transiently ischemic muscle. They did not find significant redistribution of thallium-201 in patients with uncomplicated acute myocardial infarction studied 24 to 96 hours after the onset of symptoms. However, Wackers et al.[8] reported that the maximal number of detectable thallium-201 defects occur within 24 hours of the onset of acute infarction. It follows that serial scintigraphy after a single injection of thallium-201 would be more apt to demonstrate redistribution of thallium-201 into a previous perfusion defect if serial studies were performed immediately after acute infarction. In addition, it is possible that such serial studies might give a more accurate estimate of the eventual thallium-201 defect than a single image and yet be available within hours of the patient's infarction. The purpose of this study was to determine the patterns of thallium-201 redistribution into perfusion defects when serial scintigraphy is carried out immediately after myocardial infarction.

Material and Methods

Patients: The subjects were 14 men admitted to the coronary care unit at the Veterans Administration Hospital, Dallas, Texas with a clinical diagnosis or strong suspicion of

TABLE I

Clinical Data and Summary of Scintigrams

Case no.	Age (yr)	Prior Infarction	Clinical Diagnosis	Thallium-201 Defects: Initial Scan	Thallium-201 Defects: Change on Repeat Scan	^{99m}Tc PYP Scans	Peak Serum CK (IU/ml): Max Total*	Peak Serum CK (IU/ml): CK MB
1	62	0	Inf-P MI	? L P	Same ↓	2+ P-L	556	56
2	52	0	Inf-L MI	? L P	↓ ↓	3+ P-L	234	20
3	52	0	Inf MI	? Inf P ? S	Same N Same	3+ Ant-L	168	67
4	55	P	SE MI	P	↓	3+ L	220	. . .
5	52	0	SE MI	? Inf	N	2+ Diff	162	†
6	51	0	PL MI	P	? P	3+ L	144	. . .
7	54	0	Inf MI	? Inf ? L P	↓ N Same	3+ Inf	785	. . .
8	57	? Ant	Ant MI	Ap L	N ? L	. . .	1020	. . .
9	59	Inf	Inf MI with extension	Inf P	Same Same New Ap	3+ Inf P-L	356	45
10	61	0	Ant Ap MI with inf-L extension	Inf ? S A	Same S Same New Ap	4+ Ant	928	. . .
11	39	Inf	UA	Inf ?L P	Same Same Same	. . .	18	†
12	65	Inf SE	UA	Inf P	↓ ↓	Neg	36	†
13	53	? Inf	UA	P	Same New Ap	Neg	34	†
14	72	0	Acute Ao Diss	N	Same	. . .	83	†

. . . = not done; ? = possible; ↓ = decreased.
Ant = anterior; Ao Diss = aortic dissection; Ap = apical; CK and CKMB = creatine kinase and creatine kinase MB isoenzyme, respectively; Diff = diffuse; Inf = inferior; L = lateral; MI = myocardial infarction; N = normal or resolved; Neg = negative; ^{99m}Tc PYP = technetium-99m pyrophosphate; P = posterior; S = septal; SE = subendocardial (nontransmural); UA = unstable angina.
* Upper limits of a normal male population = 80 IU/ml.
† No or insignificant (<15 IU/ml, Calbiochem document no. L06009) isoenzyme MB present as determined by the method of Rao et al.[14]

acute myocardial infarction. The age range was 39 to 72 years (mean 52). These 14 patients represented consecutive admissions when thallium-201 was available. On final diagnosis, 10 had acute myocardial infarction, 3 unstable angina pectoris and 1 acute dissecting aneurysm of the ascending aorta. Final diagnoses were assigned on the basis of historical, electrocardiographic and serum enzyme data. All patients had serial electrocardiograms and determination of serum creatine kinase, oxaloglutamic transaminase, lactic acid dehydrogenase and alpha hydroxbutyric acid dehydrogenase values for 5 or more days. A final diagnosis of either myocardial infarction or unstable angina required that the patient have pain typical of ischemic heart disease. The diagnosis of transmural myocardial infarction required development of pathologic Q waves in the electrocardiogram and elevation of at least one of the serum enzymes to twice the upper limit of normal at the expected time interval.[13] The diagnosis of subendocardial myocardial infarction required the same serum enzyme criteria in addition to electrocardiographic abnormalities consistent with myocardial ischemia (greater than 1 mm S-T segment depression with a flat or downsloping contour or greater than 5 mm T wave inversion in any lead other than aVR or V_1).

Thallium-201 myocardial scintigraphy: This procedure was performed within a mean of 1.3 hours after admission (within 2 hours for all but one patient studied at 3.9 hours) and within 6 hours (mean 4.2) of the onset of symptoms. Scintigraphy was performed at the bedside 10 minutes and then 4 to 8 hours (mean 5.7) after intravenous injection of 1 to 2 mCi thallium-201 chloride (New England Nuclear) with an Ohio Nuclear 120M mobile scintillation camera fitted with a parallel hole, low energy, high resolution collimator and adjustment of the pulse height analyzer to record the 69 to 80 kev photons with a 20 percent window. Images of 200,000 counts were obtained in anterior, 45° left anterior oblique and left lateral views. Imaging time was 6 to 12 minutes. All images were interpreted from the unprocessed Polaroid® photographs.

The images were read independently in random sequence by two of us without knowledge of the identity of the patient, the time of the study (initial or repeat) or clinical data. They were graded as normal or as showing a definite or possible perfusion defect, as previously proposed.[8] A defect was said to be present if an area of myocardium manifested no activity greater than background level. A possible defect was defined as an area with less activity than that of the patient's areas of normal uptake but more than that of background. Areas of thallium-201 defect were described as anterior, septal, apical, lateral, inferior or posterior, as described by Wackers et al.[8,9] Only complete absence of activity at the apex was considered abnormal. After interpretation of each scintigram, the initial scan for each patient was paired with the repeat scan and the two images were compared without knowledge of their temporal sequence. Any defects in the initial and repeat scans were compared and interpreted as unchanged, increased or decreased. Final interpretation was derived by a consensus reading of the two reviewers. When there was no consensus, the more normal of the two interpretations was recorded. Of the 168 segments evaluated, the observers differed on the assessment of 16 percent as follows: defect versus questionable defect (8 percent), normal area versus questionable defect (4 percent) and normal area versus defect (5 percent). Computer enhancement of the thallium-201 scintigrams was accomplished with a Hewlett-Packard 5407A Scintigraphic Data Analyzer. Computer-enhanced images were not utilized in the blinded interpretation of the images and were obtained for illustrative purposes only.

Determinations of total serum creatine kinase were performed at least daily for 5 days. In nine patients (Table I) total creatine kinase and isoenzyme MB determinations were performed on admission, as well as 4, 8, 12, 18, 24, 36, 48 and 72 hours later, according to the method of Rao et al.[14]

Scintigraphy with technetium-99m stannous pyrophosphate was performed 3 to 7 days after admission, 45 to 90 minutes after intravenous injection of 15 mCi of technetium-99m stannous pyrophosphate (technetium-99m-pertechnetate [Medi-Physics, Inc.] mixed with tetrasodium pyrophosphate with tin [An-Pyrotec, Ackerman Nuclear, Inc.]). Areas of pyrophosphate uptake were localized and rated 0 to 4^+, as described by Parkey et al.[15] The areas of pyrophosphate uptake and thallium-201 defect in the same patient were measured with calipers and compared visually. Infarct images were considered discordant in size only when discordance was unquestionably evident on visual inspection.[16]

Results

Thallium-201 scintigram: The final clinical diagnoses, interpretation of the initial and repeat thallium-201 scintigrams and the results of the pyrophosphate scintigrams are shown in Table I. Of the 14 patients with a presumed diagnosis of acute myocardial infarction, 10 subsequently met the criteria for an infarction. Three patients were considered to have unstable angina pectoris with either "crescendo angina pectoris" (Cases 11 and 13) or prolonged pain (Case 12) without objective confirmation of infarction. One patient (Case 14), the only one who died, was found at autopsy to have an acute dissecting aneurysm of the ascending aorta with hemopericardium. All but two of the patients (Cases 9 and 10) with a final diagnosis of acute myocardial infarction had a reduction in the size of at least one area of the thallium-201 perfusion defect. Typical scintigrams are illustrated in Figures 1 and 2. Between the initial and repeat studies, Patient 9 sustained an extension of his infarct and survived ventricular fibrillation and cardiopulmonary resuscitation. Patient 10 sustained an anteroapical myocardial infarction with a subsequent inferior-lateral extension. These two patients were the only subjects with a myocardial infarction whose thallium-201 defect increased in size on repeat study.

A total of 60 anatomic myocardial segments in the 10 patients with acute infarction were satisfactorily demonstrated with thallium-201 in both studies. Of these, 20 segments had either a perfusion defect or a possible perfusion defect in the initial study. Eleven of these areas of definite or possible perfusion defect were diminished or became normal at the time of the repeat study. In both patients with myocardial infarction and evidence of extension, one segment that initially appeared normal showed a perfusion defect in the repeat scan. With exclusion of these patients, of 48 satisfactorily demonstrated segments, 15 had a definite or possible perfusion defect, 11 of which decreased or resolved on the repeat study.

Correlation with serum creatine kinase: The peak serum creatine kinase and isoenzyme MB fractions of the eight patients with transmural myocardial infarction are listed in Table I. Significant elevations of serum creatine kinase and isoenzyme MB were seen in four

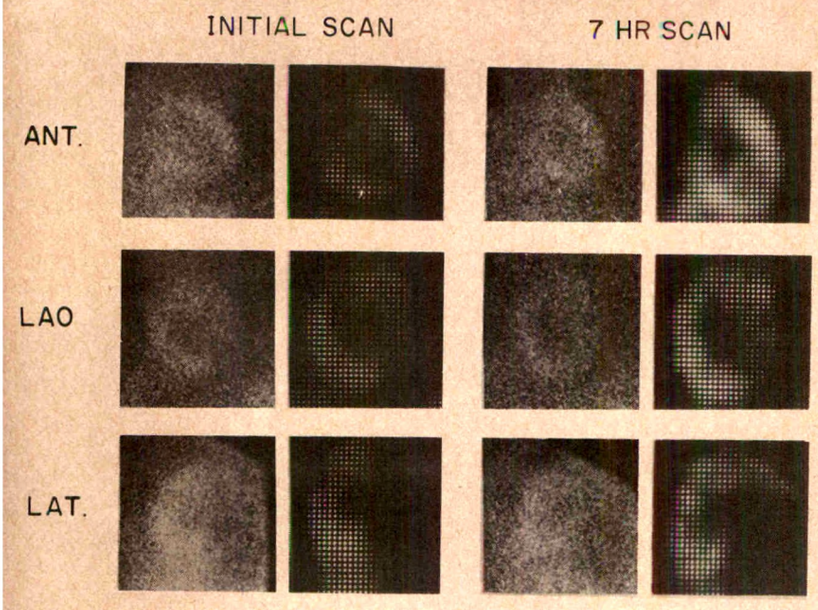

FIGURE 1. Patient 1. Initial **(left)** and repeat **(right)** thallium-201 scintigrams for the anterior, 45° left anterior oblique and lateral views. Unprocessed **(left of each pair)** and computer-enhanced **(right of each pair)** images are shown for each view. The posterior perfusion defect was decreased, and the lateral defect remained essentially unchanged 7 hours after the initial scan. ANT. = anterior; LAO = left anterior oblique; LAT. = lateral.

patients with a clinical diagnosis of acute transmural myocardial infarction but were not observed in the three patients with a diagnosis of unstable angina. The enzyme and electrocardiographic estimations of infarct size are difficult to correlate with the thallium-201 defects because the former criteria suggested an infarct of small to moderate size in seven of the eight patients with uncomplicated infarction.

Correlation with pyrophosphate scintigrams: In all patients who met the electrocardiographic and serum enzyme criteria for acute myocardial infarction the pyrophosphate scintigram was positive when obtained (Table I). Of the patients with transmural infarction, all had discrete deposition of pyrophosphate. One of the two patients with subendocardial infarction had discrete pyrophosphate uptake, and one had diffuse uptake, as previously described.[17] Of the eight patients with discrete pyrophosphate deposition, the perfusion defects noted on repeat thallium-201 scintigraphy more nearly approximated the size of the infarcted zone as defined with pyrophosphate scintigraphy than did those of the initial scan. The abnormalities of thallium-201 distribution in the initial scans were uniformly larger than those of pyrophosphate deposition in uncomplicated infarction (Fig. 3). In the two patients with other clinical evidence of infarct extension, the repeat thallium-201 image defects were larger than in the initial scintigram and best approximated the size indicated in the pyrophosphate study (Fig. 4).

Pyrophosphate scans performed in two patients with unstable angina (Cases 12 and 13) failed to demonstrate radioactive uptake. However, the results of thallium-201 scans in each patient were abnormal, both initially and on repeat study. In one of these patients, the thallium-201 perfusion defect was smaller in the repeat than in the original scan. The thallium-201 defect persisted in the repeat study in areas where these patients had previously sustained a myocardial infarction (Table I).

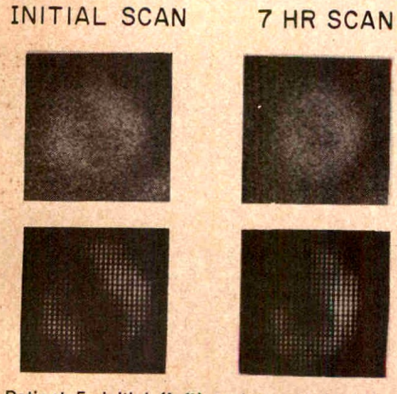

FIGURE 2. Patient 5. Initial **(left)** and repeat **(right)** unprocessed **(upper)** and computer-enhanced **(lower)** thallium-201 scintigrams from the left anterior oblique view. The inferior perfusion defect resolved 7 hours after the admission study in this patient with a clinical diagnosis of subendocardial infarction.

Discussion

Our results demonstrate the changes that may be seen when serial thallium-201 scintigraphy is performed in the immediate postmyocardial infarction period. When serial scintigraphy is performed both immediately and 4 to 8 hours after thallium-201 injection in this setting, redistribution of the thallium-201 into areas of perfusion defects may be seen when the later image is compared with the initial scan. Redistribution of thallium-201 was uniformly present in the eight patients who underwent imaging after an uncomplicated acute myocardial infarction. In these eight patients, no clinical evidence of continued myocardial damage occurred

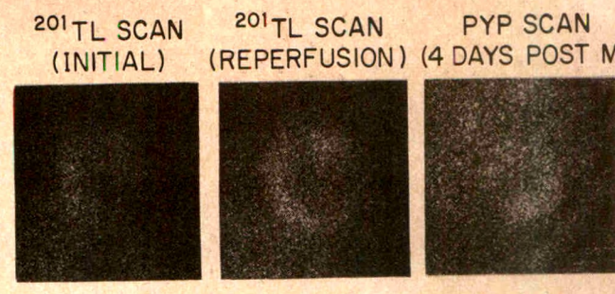

FIGURE 3. Patient 7. Left anterior oblique (LAO) view of the initial **(left)** and repeat **(middle)** thallium-201 (^{201}TL) scintigrams and the pyrophosphate (PYP) scintigram **(right)** done 4 days after myocardial infarction (MI). This patient sustained an acute inferior myocardial infarction. The initial thallium-201 scan showed possible inferior and lateral defects and a posterior defect. The repeat (reperfusion) study showed a decrease in the area of possible inferior defect and resolution of the possible lateral defect. The posterior defect was unchanged. The extent of pyrophosphate deposition more nearly corresponded to the repeat than to the initial thallium-201 defect.

between the serial images. The two patients with an increased number of perfusion defects in the thallium-201 reperfusion scan both had extension of their myocardial infarct in the interval between the initial and repeat studies. Regardless of the direction of change in thallium-201 uptake between the serial studies, the thallium-201 defect seen in the repeat or reperfusion study appeared to correspond most closely to the area of infarction defined with the pyrophosphate scan. The thallium-201 image defect observed immediately after thallium administration was uniformly larger than the area of pyrophosphate uptake if the patient had a stable course. The initial thallium defect was smaller than the pyrophosphate image in the two patients with evidence of infarct extension.

Interpretation of serial findings after myocardial infarction: The most likely explanation for our findings is that transiently ischemic but not dead myocardium slowly extracted thallium-201 from the small amount of isotope present in the circulating blood during the 4 to 8 hours that elapsed between the two scans. This explanation is consistent with the reduction in size of thallium-201 defects reported by Wackers et al.,[8] who performed scanning studies in patients 24 hours after infarction and compared the resulting image defect with that seen in scintigrams obtained within 24 hours of an acute myocardial infarction. Moreover, serial scintigraphy performed within a few hours of infarction utilizing a single thallium-201 dose appears to provide information similar to that obtained by waiting 24 hours, as judged from the concordance of the reperfusion scan defect with the area of pyrophosphate uptake. If redistribution is considered a result of slow uptake by transiently ischemic tissue,[12] serial scintigraphy after a single thallium-201 dose may overcome some of the limitations of immediate postmyocardial infarction scintigraphy because it appears to demonstrate ischemia as well as infarction and may also distinguish between them. Hence, the redistribution of thallium-201 in our patients with uncomplicated myocardial infarction may be related to the similar redistribution that occurs in ischemic but not in infarcted myocardium on exercise thallium-201 scintigraphy.[12] If this is the case, redistribution of thallium-201 into a defect in the later of the serial scans would suggest an area of transient ischemia. A defect in both the initial and repeat scans would suggest necrosis, due to either an old or an acute infarction. Likewise, failure of reperfusion or an increase in the thallium-201 defect in the later study would suggest extension of the original area of damage or the

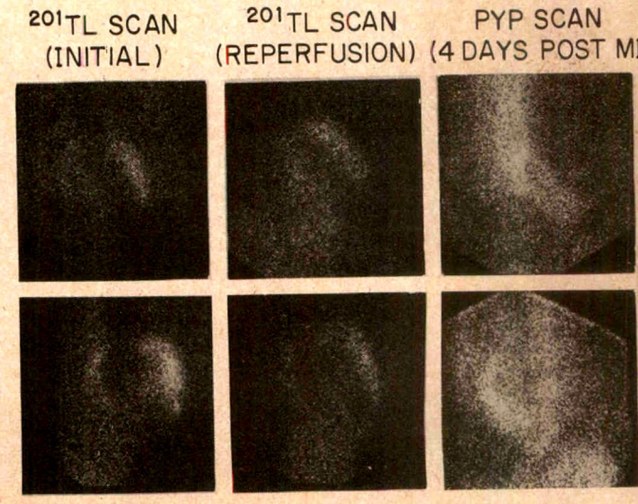

FIGURE 4. Patient 10. Anterior (ANT) and left anterior oblique (LAO) views of the initial and repeat (reperfusion) thallium-201 (^{201}TL) scintigrams and the pyrophosphate (PYP) scintigram performed 4 days after myocardial infarction (MI). This patient sustained an acute anteroapical myocardial infarction with inferolateral extension (as assessed with electrocardiography). The initial thallium-201 scan showed inferior and anterior defects and a possible septal defect. The repeat (reperfusion) study showed marked loss of apical activity, best evident in the anterior view, and the septal area had less activity than in the initial study. The extent of pyrophosphate deposition more nearly corresponded to the repeat than to the initial thallium-201 scintigraphic defect.

presence of a very limited area of periinfarction ischemia.

Wackers and his colleagues[8,9] noted that the decrease in the size of a thallium-201 defect appears to be greater in smaller than in larger infarcts when a scan within the first 24 hours after myocardial infarction is compared with a later scan. Most of our patients had a relatively small infarct area as judged from serum enzyme values, and it is possible that the differences between the initial and repeat thallium scintigrams were greater than they would have been had the infarcts been larger. Nonetheless, these preliminary observations seem promising enough to suggest a clinical usefulness for serial myocardial scintigraphy after a single thallium-201 injection carried out in the first few hours after acute myocardial infarction.

Infarction versus partial necrosis in ischemia: An alternative explanation should be considered. Buja et al.[18] reported the presence of thallium-201 in the periphery of myocardial infarcts. Although this uptake may be due to islets of normal or nearly normal myocytes with intact sodium-potassium adenosine triphosphatase scattered among necrotic cells, Buja et al. raised the possibility that, with reflow into the infarction, thallium-201 may be sequestered in an unknown way in the periphery of the infarction in the absence of an active membrane transport system. However, their data also suggest that the areas described have alterations in thallium-201 uptake that are parallel with the changes in blood flow measured with microspheres. Thus, the redistribution of thallium-201 seen in our study is consistent with the blood flow data of Buja et al. However, reflow of blood or isotope into irretrievably infarcted zones was not examined in either study. In view of the relatively similar sizes of the defects in the repeat thallium-201 postmyocardial infarction scintigrams and in the pyrophosphate scans, it appears more likely that the larger initial thallium defects represented ischemic as well as infarcted areas.

Clinical implications: There is a substantial interest in assessing the effect of various physiologic and pharmacologic interventions on myocardial infarct size.[19] Therefore, development of sensitive and accurate techniques for myocardial infarct sizing and distinguishing areas of ischemia from infarction is crucial. Serial thallium-201 imaging, when accomplished in the immediate postmyocardial infarction period, may have promise in this regard. Efficacious early interventions designed to prevent ischemic muscle from becoming necrotic might lead to greater resolution of the thallium-201 defect seen in the initial scintigram. Studies utilizing this technique as an assay of pharmacologic influence on infarct size must take care to account for any membrane-altering effects of the agent under study that may affect the myocardial concentration of potassium and metallic cations that are similarly transported.[20]

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References

1. **Zaret BL, Strauss HW, Martin ND, et al:** Noninvasive regional myocardial perfusion with radioactive potassium: study of patients at rest, exercise, and during angina pectoris. N Engl J Med 288: 809–812, 1973
2. **Strauss HW, Harrison K, Langan JK, et al:** Thallium-201 for myocardial imaging: relation of thallium-201 to regional myocardial perfusion. Circulation 51:641–645, 1975
3. **Gould KL, Hamilton GW, Lipscomb K, et al:** Method for assessing stress-induced regional malperfusion during coronary arteriography: experimental validation and clinical application. Am J Cardiol 34:557–564, 1974
4. **Nishiyama H, Sodd VJ, Adolph RJ, et al:** Intercomparison of myocardial imaging agents: ^{201}Tl, ^{129}Cs, ^{43}K, and ^{81}Rb. J Nucl Med 17:880–889, 1976
5. **Wackers FJT, Sokole EB, Samson G, et al:** Myocardial imaging in coronary heart disease with radionuclides, with emphasis on thallium-201. Eur J Cardiol 4:273–282, 1976
6. **Britten JS, Blank M:** Thallium activation of the Na^+-K^+-activated ATPase of rabbit kidney. Biochem Biophys Acta 159:160–166, 1968
7. **Ritchie JL, Trobaugh GB, Hamilton GW, et al:** Myocardial imaging with thallium-201 at rest and during exercise: comparison with coronary arteriography and resting and stress electrocardiography. Circulation 56:66–71, 1977
8. **Wackers FJT, Sokole EB, Samson G, et al:** Value and limitations of thallium-201 scintigraphy in the acute phase of myocardial infarction. N Engl J Med 295:1–5, 1976
9. **Wackers FJT, Becker AE, Samson G, et al:** Location and size of acute transmural myocardial infarction estimated from thallium-201 scintiscans: a clinicopathological study. Circulation 56:72–78, 1977
10. **Parkey RW, Bonte FJ, Stokely EM, et al:** Acute myocardial infarction imaged with ^{99m}Tc-stannous pyrophosphate and ^{201}Tl: a clinical evaluation. J Nucl Med 17:771–779, 1976
11. **Henning H, Shelbert HR, Righetti A, et al:** Dual myocardial imaging with technetium-99m pyrophosphate and thallium-201 for detecting, localizing and sizing acute myocardial infarction. Am J Cardiol 40:147–155, 1977
12. **Pohost GM, Zir LM, Moore RH, et al:** Differentiation of transiently ischemic from infarcted myocardium by serial imaging after a single dose of thallium-201. Circulation 55:294–302, 1977
13. **Sobel BE, Shell WE:** Serum enzyme determinations in the diagnosis and assessment of myocardial infarction. Circulation 45: 471–482, 1972
14. **Rao PS, Lukes JJ, Ayres SM, et al:** New manual and automated method for determining activity of creatine kinase isoenzyme MB, by use of dithiothreitol: clinical applications. Clin Chem 21: 1612–1618, 1975
15. **Parkey RW, Bonte FJ, Meyer SL, et al:** A new method for radionuclide imaging of acute myocardial infarction in humans. Circulation 50:540–546, 1974
16. **Berger HJ, Gottschalk A, Zaret BL:** Dual radionuclide study of acute myocardial infarction: comparison of thallium-201 and technetium-99m stannous pyrophosphate imaging in man. Ann Intern Med 88:145–154, 1978
17. **Willerson JT, Parkey RW, Bonte FJ, et al:** Technetium stannous pyrophosphate myocardial scintigrams in patients with chest pain of varying etiology. Circulation 51:1046–1052, 1975
18. **Buja LM, Parkey RW, Stokely EM, et al:** Pathophysiology of technetium-99m stannous pyrophosphate and thallium-201 scintigraphy of acute anterior myocardial infarcts in dogs. J Clin Invest 57:1508–1522, 1976
19. **Maroko PR, Braunwald E:** Modification of myocardial infarction size after coronary occlusion. Ann Intern Med 79:720–733, 1973
20. **Schelbert HR, Ashburn WL, Chauncey DM, et al:** Comparative myocardial uptake of intravenously administered radionuclides. J Nucl Med 15:1092–1100, 1974

Results of Aortocoronary Bypass Grafting in Patients With Subendocardial Infarction: Late Follow-Up

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Twenty-eight patients with subendocardial infarction (Group A) were compared with 28 patients with unstable angina (Group B) and 28 with stable angina (Group C) matched for age and sex. The three groups did not differ in prevalence of diabetes, hypertension, old infarction or duration of disease. There were no significant differences in number of diseased vessels, coronary score, abnormal left ventricular wall motion or left ventricular end-diastolic pressure. Angiograms performed 2 weeks postoperatively revealed closure of 3 of 31 grafts (16 patients) in Group A, closure of 3 of 34 grafts (17 patients) in Group B and closure of 6 of 50 grafts (22 patients) in Group C (differences not significant). Postoperative angiograms showed improved wall motion in 37 percent of Group A, 53 percent of Group B and 36 percent of Group C (differences not significant). Postoperative new Q waves appeared in one patient in Group A and in two patients in Groups B and C. There were no hospital or late deaths. In a mean follow-up period of 29 months, 68 percent of patients in Group A, 61 percent in Group B and 54 percent in Group C were asymptomatic. Thus, bypass grafting was performed with similarly low mortality and morbidity in patients with subendocardial infarction and in those with angina; more than one third of postoperative angiograms in the three groups showed improved wall motion; and late follow-up studies demonstrated functional improvement in the majority of patients in all three groups.

The course of coronary artery disease is unpredictable in any individual patient with angina pectoris. However, in recent years, studies[1–5] have shown that in some patients "stable" angina passes through the stages of "unstable," "progressive" or "preinfarction" angina before a transmural or subendocardial infarction develops. After the initial controversies concerning prognosis in surgically treated patients with unstable angina,[1–5] several studies[6–8] indicated not only symptomatic improvement but also longer survival after bypass surgery. However, Hutter et al.[9] found that such patients had a greater incidence of new Q waves than medically treated patients and no improvement in survival. There is disagreement[10–13] whether bypass surgery, in addition to alleviating symptoms, prolongs survival in patients with stable angina.

Among patients with subendocardial infarction, those treated medically have shown a 10 to 37 percent rate of transmural infarction[14–17] and a 0 to 18 percent mortality rate within 4 weeks[18–20] and a 3 to 14 percent yearly mortality rate after hospital discharge.[2,16,20,21] Similarly, both a high yearly rate of transmural myocardial infarction and a high mortality rate have been found in patients who are admitted to a coronary care unit with symptoms of myocardial infarction but whose electrocardiogram did not confirm the diagnosis.[22–24]

In this report we present our experience with coronary bypass surgery in 28 patients with subendocardial infarction and in an equal number of patients with unstable and stable angina pectoris who were followed up postoperatively for a mean period of 29 months.

Material and Methods

Patients

Among 800 patients undergoing saphenous vein bypass graft surgery between January 1972 and July 1977 at this institution, 28 had preoperative subendocardial infarction. These patients (Group A) were compared with 28 patients

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with unstable angina pectoris (Group B) and 28 patients with stable (Group C) angina pectoris who were matched for age and sex. Almost all patients in the group with subendocardial infarction were admitted to the hospital from the emergency room with a history of chest pain lasting more than 30 minutes and findings of symmetric T wave inversion with or without S-T segment depression. They were observed in the coronary care unit to rule out transmural infarction. A few patients with similar continuous angina were transferred from the coronary care unit of other hospitals because of electrocardiographic evidence of subendocardial infarction and significant enzyme elevations. After 24 to 48 hours of observation in our hospital, if transmural infarction did not develop, coronary angiography was performed.

The criteria for subendocardial infarction included (1) angina pectoris at rest lasting more than 15 minutes; (2) elevation of at least two of three serum enzymes (creatine kinase, serum glutamic oxaloacetic transaminase or lactic dehydrogenase) to at least twice normal values or greater; (3) T wave inversion or S-T segment depression, or both, lasting more than 48 hours without pathologic Q waves.

The criteria for unstable angina were those previously reported.[3] The group with stable angina met New York Heart Association[25] criteria for class II to IV angina pectoris without acute electrocardiographic changes and symptoms relieved with rest or sublingual nitroglycerin. Most of these patients had progressive angina. Patients were excluded if they were undergoing left ventricular aneurysmectomy, prosthetic valve replacement or repair of associated congenital heart defect in addition to bypass grafting or if they had bundle branch block.

Studies

Hemodynamic studies were performed after an overnight fast, after all medications except nitroglycerin and long-acting nitrates had been discontinued for at least 24 hours.

Left and right heart catheterization and left ventricular and selective coronary angiography, using the Judkins[26] or Sones and Shirey[27] techniques, were performed in all patients. In quantitating left ventricular dysfunction and the patterns of left ventricular contraction, we used the techniques and principles previously reported,[28] utilizing the descriptive terminology suggested by Herman et al.[29] The severity and extent of coronary disease were graded according to the criteria of Bruschke et al.[30] All angiograms and electrocardiograms were reviewed by two cardiologists and accepted for study only if there was complete agreement on interpretation. Twelve lead electrocardiograms were performed in each patient on admission and on the day before cardiac catheterization. In addition, patients with subendocardial infarction or unstable angina had electrocardiograms performed daily and also immediately after cardiac catheterization to rule out the occurrence of transmural infarction during the procedure. This precaution was taken because several of the patients with subendocardial infarction had additional anginal attacks after ventriculography or coronary angiography. A normal resting electrocardiogram was defined with conventional criteria.[31]

Coronary revascularization was performed after completion of cardiac catheterization in all patients with subendocardial infarction and unstable angina with significant coronary obstruction. The patients were transferred directly from the catheterization laboratory to the operating room. Repeat left heart catheterization and selective graft angiography were performed 2 to 3 weeks after surgery in all patients giving consent.

TABLE I

Clinical Profile

	Group A: Subendocardial Infarction		Group B: Unstable Angina		Group C: Stable Angina	
	no.	%	no.	%	no.	%
Patients*	28	100	28	100	28	100
Sex						
Male	23	82	23	86	23	82
Female	5	18	5	14	5	18
History of infarction	9	32	11	39	12	43
Evidence of infarction in electrocardiogram	8	29	11	39	8	29
History of hypertension	8	29	8	29	8	29
History of diabetes	3	11	3	11	6	21
Angina pectoris						
<1 year	15	54	11	39	9	32
1–5 years	7	25	11	39	9	32
>5 years	6	21	6	21	10	36

* In all three groups, the patients had a mean age (± standard deviation) of 53 ± 8 years (range 34 to 72 years).

Results

Of 800 patients with coronary artery disease who underwent saphenous vein bypass surgery, 28 had subendocardial infarction (Group A). These patients were compared with 28 patients with unstable (Group B) and 28 with stable (Group C) angina. Age, sex, prevalence of diabetes mellitus, hypertension, old myocardial infarction or duration of disease did not differ among the three groups (Table I). No significant differences in the number of diseased vessels, coronary score, abnormal left ventricular wall motion, elevated pulmonary wedge or left ventricular end-diastolic pressures were found in these three groups (Table II). Angiograms obtained 2 weeks after operation revealed closure of 3 of 31 grafts (10 percent) in 16 patients in Group A, closure of 3 of 34 grafts (9 percent) in 17 patients in Group B, and closure of 6 of 55 grafts (11 percent) in 22 patients in Group C (differences not significant). The postoperative study revealed improved left ventricular wall motion in 6 patients (37 percent) in Group A, 9 patients (53 percent) in Group B and 8 patients (36 percent) in Group C (differences not significant). Wall motion was unchanged in 8 patients (50 percent) in Group A, in 6 (35 percent) in Group B and 13 (59 percent) in Group C. Only 2 patients (13 percent) in Group A, 2 (12 percent) in Group B and 1 (4 percent) in Group C manifested postoperative deterioration of the left ventricular segmental wall motion.

New Q waves appeared perioperatively in one patient in Group A and in two patients each in Groups B and C (difference not significant). One patient in Group B had a postoperative cerebrovascular accident with left-sided hemiplegia. Three patients each in Group B and C and one in Group A had postoperative pulmonary emboli that responded to systemic anticoagulation. A postpericardiotomy syndrome occurred in one patient each in Groups A and C, requiring steroid therapy in one.

TABLE II

Angiographic Data

Patients	Group A: Subendocardial Infarction no.	%	Group B: Unstable Angina no.	%	Group C: Stable Angina no.	%
Coronary artery disease*	28	100	28	100	28	100
Single	10	36	3	11	6	21
Double	8	29	15	54	7	25
Triple	10	36	10	36	15	59
RCA	17	61	16	57	19	68
LAD	26	93	27	96	26	93
LCx	13	46	20	71	20	71
LCA	4	14	4	14	0	0
Abnormal LV angiogram (preop)	21	75	21	75	16	57
Elevated pulmonary wedge pressure ≤ 12 mm Hg	2	7	2	7	3	11
Elevated left ventricular end-diastolic pressure ≤ 12 mm Hg	14	50	11	39	11	39

* Patients in Groups A, B and C had a coronary score (mean ± standard deviation) of 9 ± 3, 10 ± 3 and 10 ± 3, respectively.

LAD = left anterior descending coronary artery; LCA = left main coronary artery; LCx = left circumflex artery; LV = left ventricular; preop = preoperative; RCA = right coronary artery.

There were no hospital or late deaths. During a mean follow-up period of 29 months (range 5 to 64), a transmural infarction developed in one patient in Group B. One patient in Group A and two in Group C underwent reoperation because of recurrence of angina pectoris at rest. At the end of the follow-up period, 68 percent of patients in Group A were in New York Heart Assocation class I and 29 percent in class II–III. In Group B, 61 percent were in class I and 36 percent in class II–III. In Group C, 54 percent were in class I and 43 percent in class II–III.

Discussion

Natural history of subendocardial infarction: The hospital course and subsequent follow-up of patients with nontransmural (subendocardial) infarction have shown that this entity is treacherous, with a significant incidence of transmural infarction and death.[3,4,32] Indeed, several studies[19–21] have indicated that the natural history of subendocardial infarction does not differ significantly from that of classic transmural infarction. Madigan et al.[16] showed, in a mean follow-up period of 11 months, that of 50 patients with subendocardial infarction 46 percent had unstable angina and only 24 percent were asymptomatic with medical therapy. In 6 of 28 patients (21 percent) receiving medical therapy a transmural infarction developed, and 1 patient (3 percent) died. Levy and associates[21] noted, in a mean follow-up period of 35 months, that sudden death and recurrent infarction occurred twice as often in patients with a nontransmural infarction as in those with a transmural infarction. Others[22,24] have reported that patients with prolonged ischemic chest pain, but without evidence of transmural infarction, had a yearly mortality rate of 10 to 13 percent.

Bypass surgery in unstable and stable angina: Recent comparisons of the incidence of myocardial infarction and long-term mortality in patients with unstable angina receiving medical therapy and in similar patients undergoing bypass surgery revealed a lower yearly mortality in the surgical group as well as greater symptomatic improvement.[6,7] Whether patients with unstable angina have greater perioperative mortality is controversial.[3,8,32] Surgical mortality in patients with unstable angina depends on selection and surgical expertise and thus varies greatly from institution to institution.[3,32,33]

The beneficial results of coronary bypass surgery in patients with stable angina remains controversial. Several reports indicated not only better symptomatic improvement in the surgical treatment group with multivessel coronary disease but also a lower yearly mortality after 2 to 7 year follow-up, when compared with nonrandomized medical treatment groups.[10,11,34–38] However, the randomized Veterans Administration Cooperative Study, after a 3 year follow-up of 310 medically treated patients and 285 with coronary bypass showed no prolongation of life in the surgical group, an operative mortality rate of 5.6 percent and a yearly mortality rate of 4 percent.[13]

Bypass surgery in subendocardial infarction: Our results in 28 patients indicate that coronary bypass surgery can be performed in patients with subendocardial infarction. The mortality and perioperative morbidity of this group are not different from those of patients with unstable or stable angina, and the majority of patients are asymptomatic after surgery. Bypass grafting is not recommended in acute transmural infarction because of definitely increased mortality as well as experimental evidence that reperfusion of acute infarcts leads to larger zone hemorrhage and necrosis.[38]

The absence of mortality in our 28 surgically treated patients with subendocardial infarction and their generally benign postoperative course differ significantly from the reported surgical experience in patients with classic transmural infarction. Clearly, the areas of infarction, although sufficient to produce diagnostic enzyme and electrocardiographic abnormalities, were not so extensive or confluent as to result in significant infarct extension after bypass surgery. The incidence rate of perioperative Q waves did not differ significantly in the group with subendocardial infarction and those with unstable or stable angina (4 versus 7 percent), suggesting that the areas of actual infarction were small. Larger areas might be expected to extend postoperatively sufficient to present as postoperative Q waves. Madigan et al.[39] reported a similar experience with surgically treated patients with subendocardial infarction. Among their 28 patients, perioperative new Q waves developed in 10.7 percent, and one patient (3.6 percent) died. In a mean follow-up period of 16 months,

78 percent were free of angina pectoris and there were no late deaths or infarctions.

Perhaps the most significant observation regarding the efficacy of bypass grafting in our group with subendocardial infarction is the improved ventricular contractile pattern in 37 percent of patients, an incidence rate identical with that of the group with stable angina.

None of our patients had technetium pyrophosphate scans before or after bypass surgery. Therefore, we do not know whether such scans would have shown any difference between the group with subendocardial infarction and that with stable angina.

If the results in this small series are extended and confirmed, coronary bypass grafting could be considered an effective method for preserving ischemic myocardium, relieving symptoms and prolonging life in patients with subendocardial infarction.

References

1. **Gazes PC, Mobley EW Jr, Faris HW Jr, et al:** Preinfarction (unstable) angina—a prospective study—ten year follow-up. Prognostic significance of electrocardiographic changes. Circulation 48:331–337, 1973
2. **Fishl SJ, Herman MV, Gorlin R:** The intermediate coronary syndrome: clinical, angiographic and therapeutic aspects. N Engl J Med 288:1193–1198, 1973
3. **Wisoff BG, Aintablian A, Hartstein ML, et al:** Unified diagnostic and surgical approach for unstable angina. Ann Thorac Surg 18: 472–478, 1974
4. **Conti RC, Gilbert JB, Hodges M, et al:** Unstable angina pectoris: randomized study of surgical versus medical therapy (abstr). Am J Cardiol 35:129, 1975
5. **Selden R, Neil WA, Ritzmann LW, et al:** Medical versus surgical therapy for acute coronary insufficiency. A randomized study. N Engl J Med 293:1329–1333, 1975
6. **Bertolasi EA, Tronge JE, Riccitelli MA, et al:** Natural history of unstable angina with medical or surgical therapy. Chest 70: 596–605, 1976
7. **Hultgren HN, Pfeifer JF, Angell WW, et al:** Unstable angina: comparison of medical and surgical management. Am J Cardiol 39:739–740, 1977
8. **Wiles JC, Peduzzi PN, Hammond GL, et al:** Preoperative predictors of operative mortality for coronary bypass grafting in patients with unstable angina pectoris. Am J Cardiol 39:939–943, 1977
9. **Hutter AM Jr, Russell RO Jr, Resnekov L, et al:** Unstable angina pectoris. National randomized study of surgical versus medical therapy: results in 1, 2 and 3 vessel disease (abstr). Circulation 55, 56:Suppl III:III–60, 1977
10. **Sheldon WC, Rincon G, Effler DB, et al:** Vein graft surgery for coronary artery disease. Survival and angiographic results in 1,000 patients. Circulation 47, 48:Suppl III:III-184–III-189, 1973
11. **McNeer JF, Starmer CF, Bartel AG, et al:** The nature of treatment selection in coronary artery disease. Experience with medical and surgical treatment of a chronic disease. Circulation 49:606–614, 1974
12. **Stiles RR, Lindesmith GG, Tucker BL, et al:** Long-term follow-up of patients with coronary artery bypass grafts. Circulation 54:Suppl III:III-32–III-34, 1976
13. **Murphy ML, Hultgren HN, Detre K, et al:** Treatment of chronic stable angina: a preliminary report of survival data of randomized Veterans Administration cooperative study. N Engl J Med 297: 621–627, 1977
14. **Madigan NP, Rutherford BD, Frye RL:** Clinical course and coronary anatomy of subendocardial infarction (abstr). Am J Cardiol 35:154, 1975
15. **Genovese MG, Salaki JS, Kennedy RJ, et al:** Subendocardial infarction: what happens later. Chest 92:542–543, 1965
16. **Madigan NP, Rutherford BD, Frye RL:** The clinical course, early prognosis and coronary anatomy of subendocardial infarction. Am J Med 60:634–641, 1976
17. **Kossowsky WA, Mohr B, Rafii S, et al:** Superimposition of transmural infarction following acute subendocardial infarction. How frequent? Chest 69:758–761, 1976
18. **Scheinman MM, Abbott JA:** Clinical significance of transmural versus nontransmural electrocardiographic changes in patients with acute myocardial infarction. Am J Cardiol 55:602–613, 1973
19. **Madias JE, Chahine RA, Gorlin R, et al:** A comparison of transmural and nontransmural acute myocardial infarction. Circulation 49:498–507, 1974
20. **Rigo P, Murray M, Taylor DR, et al:** Hemodynamic and prognostic findings in patients with transmural and nontransmural infarction. Circulation 51:1064–1070, 1975
21. **Levy WK, Cannom DS, Cohen LS:** Prognosis of subendocardial myocardial infarction. Circulation 51:Suppl II:II-107, 1975
22. **Dussia EE, Cromartie D, McCraney J, et al:** Myocardial infarction with and without laboratory documentation. One year prognosis. Am Heart J 92:148–151, 1976
23. **Pitt B:** IV. Natural history of myocardial ischemic damage. Natural history of myocardial infarction and its prodromal syndromes. Circulation 53:Suppl I:I-132–I-140, 1976
24. **Schroeder JS, Lamb IH, Harrison DC:** Patients admitted to the coronary care unit for chest pain: high risk subgroup for subsequent cardiovascular death. Am J Cardiol 39:829–832, 1977
26. **Judkins MP:** Selective coronary arteriography. I. A percutaneous transfemoral technique. Radiology 89:815–824, 1967
27. **Sones M, Shirey EK:** Cine coronary arteriography. Mod Concepts Cardiovasc Dis 31:735–738, 1962
28. **Aintablian A, Hamby RI, Garsman J:** Correlation of heart size with clinical and hemodynamic findings in patients with coronary artery disease. Am Heart J 91:21–27, 1976
28. **Herman MV, Heinle RA, Klein MD, et al:** Localized disorders in myocardial contraction. Asynergy and its role in congestive heart failure. N Engl J Med 277:222–232, 1967
29. **Bruschke AVG:** The diagnostic significance of the coronary arteriogram. A study of its value in relation to other diagnostic methods. Utrecht, Kremink en Zovn, NV, 1970
30. **Simonson E:** Differentiation between normal and abnormal in electrocardiography. Saint Louis, CV Mosby, 1961
31. **Klein MS, Ludbrook PA, Mimbs JW, et al:** Perioperative mortality rate in patients with unstable angina selected by exclusion of myocardial infarction. J Thorac Cardiovasc Surg 73:253–257, 1977
32. **Dunkman BW, Perloff JK, Kastor JA, et al:** Medical prospectives in coronary artery surgery—a caveat. Ann Intern Med 81:817–837, 1974
33. **Pichard A:** Coronary arteriography for everyone? Am J Cardiol 38:533–535, 1976
34. **Ullyot DJ, Wisneski J, Sullivan RW, et al:** Improved survival after coronary artery surgery in patients with extensive coronary artery disease. J Thorac Cardiovasc Surg 70:405–413, 1975
35. **Sheldon WC, Rincon G, Pichard AD, et al:** Surgical treatment of coronary artery disease: pure graft operations with a study of 741 patients followed 3–7 years. Prog Cardiovasc Dis 18:237–253, 1975
36. **Duvoisin GE, Rudy LW, Ganji JM, et al:** Direct coronary artery surgery for prolonged survival in triple vessel coronary artery disease. Circulation 51, 52:Suppl II:II-176, 1975
37. **Manley D, Friedberg HD, Auer J, et al:** Late follow-up (five years) after coronary artery surgery in comparison to reported medical series (abstr.) Am J Cardiol 35:155, 1975
38. **Bresnahan GF, Roberts R, Shell ME, et al:** Deleterious effects due to hemorrhage after myocardial reperfusion. Am J Cardiol 33: 82–86, 1974
39. **Madigan NP, Rutherford BD, Barnhorst DA, et al:** Early saphenous vein grafting after subendocardial infarction: immediate surgical results and late prognosis (abstr). Circulation 53, 54:Suppl II:II-36, 1977

Intraoperative Evaluation of the Functional Significance of Coronary Collateral Vessels in Patients With Coronary Artery Disease

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Coronary hemodynamics were studied intraoperatively in 65 patients undergoing aortocoronary bypass grafting. Poststenotic coronary pressure and graft flow hyperemia were measured. Patients without coronary collateral vessels on arteriography (class A) were compared with patients with collateral vessels (class B). Patients in class A were grouped according to the angiographically determined degree of coronary stenosis. Eight of these patients with moderate coronary stenosis underwent intraoperative studies with transient complete coronary occlusion and were classified in the "acute" occlusion group. In class B all patients had complete coronary occlusion with good retrograde filling of the distal segment.

In class A patients there was good correlation between the degree of stenosis and poststenotic pressure or hyperemic response. Stenosis had to be at least 80 percent before it produced a significant pressure gradient or graft flow hyperemia. In class B patients (those with complete "chronic" coronary occlusion), poststenotic pressure was significantly greater than in the class A patients with "acute" occlusion, significantly less than in the class A groups with 71 to 80 percent and 81 to 90 percent stenosis but not significantly different from values in the class A group with 91 to 99 percent stenosis. The hyperemic response was significantly less than in the "acute" occlusion group of class A, significantly greater than in the class A groups with 71 to 80 percent and 81 to 90 percent stenosis, but not significantly different from values in the class A group with 91 to 99 percent stenosis.

It is concluded that (1) under basal conditions a coronary stenosis must be at least 80 percent to be hemodynamically significant, and (2) well developed collateral vessels produce in a completely occluded coronary artery hemodynamic changes that simulate those of a 90 percent coronary stenosis without collateral vessels.

One problem in assessing critical coronary stenosis is the development of coronary collateral vessels in the presence of severe stenosis or occlusion of the coronary vessels. Collateral vessels reduce the degree of coronary stenosis to some extent and probably can change a "critical" to a "subcritical" stenosis.[1,2] On the other hand, quantitative hemodynamic assessment of "critical" coronary stenosis itself is difficult in man, mainly because of technical problems in the exact determination of regional coronary flow. With myocardial imaging techniques using indium-113m macroaggregated albumin, potassium-43 or thallium-201, for example, only semiquantitative results can be obtained,[3-5] and with xenon-133 scintigraphy serious limitations are encountered in determining coronary collateral flow.[6]

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TABLE I

Patients and Groups

Group	Percent Coronary Stenosis	Grafts (no.) Total	LAD	RC	LCx	LM	LD	Patients (no.)
	Class A (without collateral vessels)							
1A	>70–≤80	11	5	2	2	1	1	11
2A	>80–≤90	23	13	6	1	2	1	22*
3A	>90–<100	21	18	2	0	1	0	21
4A	100 (acute)	8	6	2	0	0	0	8†
	Class B (with collateral vessels)							
B	100 (chronic)	11	6	4	0	1	0	11

* In one of these patients two grafts were studied.
† Of these eight patients, seven are also included in group 1A and one is also included in group 2A.
LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LD = diagonal branch of the left anterior descending coronary artery; LM = marginal branch of the left circumflex coronary artery; RC = right coronary artery.

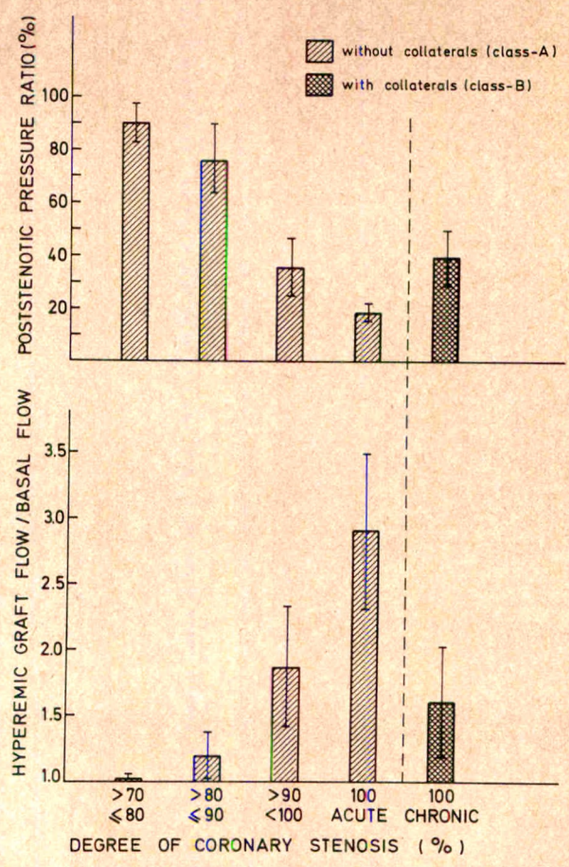

FIGURE 1. Coronary hemodynamics in relation to the degree of proximal coronary stenosis. **Upper panel,** relation between poststenotic pressure ratio and the percent of coronary stenosis. **Lower panel,** relation between hyperemic graft flow response and the degree of coronary stenosis. Mean values ± standard deviation are depicted. The statistical significance of the differences between groups is presented in Table II.

Direct measurements of pressure and flow over the stenotic coronary segment should be the best approach, but these measurements are still in the domain of the experimental laboratory. Nevertheless, aortocoronary bypass surgery provides one of the best opportunities to study the coronary vascular system in man.[7] Under conditions of technically perfect anastomosis, basal graft flow, hyperemic flow response after temporary closure of the graft and pressure measurements in the graft before and during transient graft occlusion provide useful information about coronary hemodynamics. With this approach, this study describes quantitatively (1) the effects of progressive coronary arterial obstruction on coronary hemodynamics in patients with coronary artery disease, and (2) the functional significance of coronary collateral vessels. The latter data were obtained by comparing the coronary hemodynamics in a complete coronary occlusion with compensatory collateral vessels with the hemodynamics in "pure" stenosis.

Material and Methods

Patients

Sixty-five patients, 59 men and 6 women, with coronary artery disease were studied. Selective coronary arteriography was performed in all patients 3 months or less before coronary arterial surgery. The degree of coronary stenosis was measured from the arteriogram according to the method of Brown et al.[8] Coronary collateral vessels were estimated as described by Hamby et al.[2] Left ventricular systolic wall motion was assessed preoperatively from review of the biplane left ventriculogram.

Before the intraoperative hemodynamic studies were performed the patients were classified into two major categories (Table I): Class A, patients without angiographically visible coronary collateral channels to the vessel that was later bypassed, and class B, patients with angiographically visible coronary collateral channels to that vessel. Patients in both classes were further grouped according to the angiographically determined degree of coronary stenosis:

Class A: There were four groups in class A: *group 1,* stenosis of 71 to 80 percent (11 patients, 11 grafts studied); *group 2,* stenosis of 81 to 90 percent (22 patients, 23 grafts studied); *group 3,* stenosis of 91 to 99 percent (21 patients, 21 grafts studied); and *group 4,* complete "acute" coronary occlusion. Because none of the patients in class A had a complete coronary occlusion due to progressive sclerosis, we produced an acute experimental coronary occlusion in seven patients in group 1A and in one patient in group 2A with an 82 percent stenosis.

Class B: All patients in this class had a complete coronary occlusion with angiographically visible collateral vessels. This group will be referred to as the group with "chronic" occlusion."

Surgical Procedures

Operation was performed with the patient on cardiopulmonary bypass, utilizing a disposable bubble-type oxygenator. After institution of the bypass, the distal anastomosis between the coronary artery and the saphenous vein was performed during cardioplegic arrest. Coronary perfusion was then re-

TABLE II

Coronary Hemodynamics in Progressive Coronary Stenosis (mean ± SD)

Group	Percent Coronary Stenosis	Hyperemic/ Basal Flow Ratio	Duration of Hyperemia (sec)*	Dipyridamole/ Basal Flow Ratio	PSPR (%)	PRP (mm Hg·min^{-1})
			Class A (without collateral vessels)			
1A	>70–≤80	1.02 ±0.05 no. = 11	1.5 +2.5 no. = 11	2.30 ±0.72 no. = 6	90.2 ±7.1 no. = 5	11,098 ±3,567 no. = 11
2A	>80–≤90	1.21 ±0.18 no. = 23 P <0.001	9.2 ±6.8 no. = 23 P <0.001	2.33 ±0.71 no. = 13 NS	76.2 ±11.8 no. = 11 P <0.05	11,565 ±3,935 no. = 23 NS
3A	>90–<100	1.88 ±0.46 no. = 21 P <0.001	28.7 ±17.3 no. = 21 P <0.001	2.28 ±0.73 no. = 13 NS	35.8 ±10.8 no. = 13 P <0.001	14,755 ±4,754 no. = 21 NS
4A	100 (acute)	2.92 ±0.67 no. = 8 P <0.01	28.3 ±9.3 no. = 7 NS	2.75 ±0.75 no. = 3 NS	18.9 ±3.5 no. = 8 P <0.001	12,722 ±5,221 no. = 8 NS
			Class B (with collateral vessels)			
B	100 (chronic)	1.62 ±0.43 no. = 11 P <0.01 NS†	18.1 ±7.8 no. = 10 P <0.05 P <0.05†	2.22 ±0.65 no. = 9 NS NS†	40.2 ±10.5 no. = 10 P <0.001 NS†	12,302 ±2,862 no. = 11 NS NS†

* In two patients (one in group 4A and one in class B) the graft flow hyperemia was not measured until return to baseline values; thus the duration of hyperemia could not be measured in these cases.

NS = not statistically significant (probability >0.05); P (probability) = significance of difference from preceding group; P† = significance of difference from group 3A; PRP = pressure-rate product; PSPR = poststenotic pressure ratio; SD = standard deviation.

stored and the proximal anastomosis performed. Approximately 30 minutes after termination of the anastomosis and before closure of the chest, graft flow was measured with a Hellige pulsed square wave electromagnetic flowmeter. The transducers were calibrated in vitro with pooled blood. Mean values for flow were determined with electromagnetic damping. Arterial blood pressure was measured with a Statham pressure transducer. In 47 cases coronary pressure was measured with use of a small PVC tube inserted into a side branch of the vein that was not ligated during preparation of the saphenous vein graft. The PVC tubing was connected to a Statham pressure transducer. Graft flow, arterial and coronary pressure and electrocardiographic lead II were recorded on a Hellige 6 channel direct writing system.

Reactive hyperemia was produced by occluding the vein graft for 20 seconds with a rubber-tipped forceps. Seven patients in group 1A and one patient in group 2A underwent an additional procedure: The coronary artery was dissected free between the coronary stenosis and the graft anastomosis and occluded with a rubber tourniquet for 20 seconds. In these patients peripheral coronary pressure was also recorded by way of the graft during graft clamping. In 44 grafts, dipyridamole (total dose 10 mg) was injected through the side branch catheter into the graft and graft flow measured.

The significance of the results was tested by means of the t test for paired values within groups and for unpaired values between groups.

Design of Study

Class A patients: To estimate coronary hemodynamics in progressive coronary sclerosis, the following determinations were made: (1) the relation between poststenotic coronary pressure and the degree of stenosis; (2) the relation between hyperemic graft flow response and the degree of stenosis; and (3) the relation between maximal graft flow and the degree of stenosis.

Class B patients: Coronary hemodynamic changes in patients with "collateralized" complete coronary obstruction were compared with those in patients with different degrees of "pure" coronary stenosis. The studies included (1) comparison of poststenotic or peripheral coronary pressure in class B with the corresponding values in the different groups in class A; and (2) comparison of hyperemic graft flow response in class B with the corresponding values in the different groups in class A. The objective of these comparisons was to assess the degree of "pure" coronary stenosis (stenosis without angiographically visible collateral vessels) that is simulated by the coronary hemodynamic changes produced by collateral vessels in complete coronary obstruction.

Results

Coronary hemodynamics in progressive coronary stenosis: The results of pressure and flow measurements are depicted in Figure 1. The upper panel presents the relation between poststenotic coronary pressure and the degree of coronary stenosis. Poststenotic coronary pressure was expressed as a ratio: diastolic poststenotic coronary pressure/diastolic systemic pressure × 100. This poststenotic pressure ratio was significantly less in group 2A than in group 1A (probability [P] <0.05); however, the real difference in poststenotic pressure occurred between groups 2A and 3A (76 versus 35.8 percent) (P <0.001). In group 4A (complete "acute" occlusion), poststenotic pressure decreased further to 18.9 percent (P <0.001) (Table II).

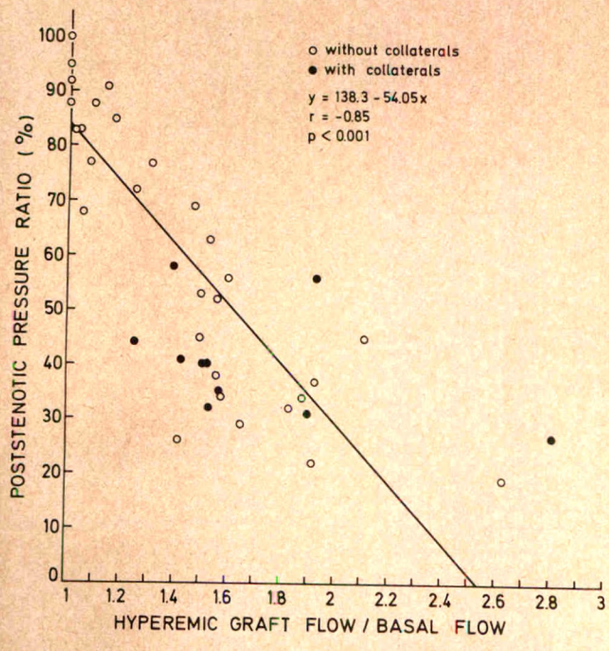

FIGURE 2. Relation between poststenotic coronary pressure and reactive hyperemic graft flow response in progressive coronary sclerosis. A linear regression was calculated for all data points except the group with experimental acute occlusion (4A). The regression was statistically significant ($P < 0.001$), and the correlation coefficient was 0.85. Patients with coronary collateral channels (group B) are identified by the **closed circles**; patients without collateral vessels are indicated by the **open circles**.

The lower panel of Figure 1 shows the relation between hyperemic graft flow response (peak hyperemic flow/basal graft flow) and the degree of coronary stenosis. In group 1A (71 to 80 percent stenosis), almost no hyperemic response was found, but the response increased significantly with progressive coronary narrowing to the point of complete occlusion. Patients in group 4A (acute coronary occlusion) had the highest value for hyperemic graft flow (2.92). The duration of the hyperemic response increased with progressive stenosis (groups 1A to 3A). However, complete occlusion of the coronary artery did not further prolong the duration of the response: Groups 3A and 4A did not differ significantly from each other ($P > 0.05$).

Maximal graft flow was tested in several patients in each group after intracoronary injection of dipyridamole. Regardless of the degree of stenosis, graft flow increased approximately two times over the basal flow level. In all instances, except in acute occlusions, graft flow after dipyridamole was significantly greater than peak hyperemic flow ($P < 0.01$). In patients with acute occlusion, the difference between the two values was not significant ($P > 0.05$ for paired sets of observations). Mean values for the increase in graft flow (graft flow after dipyridamole/basal graft flow) are listed in Table II. None of these values differed significantly among groups ($P > 0.05$).

Poststenotic pressure ratio in class B was significantly less than the corresponding value in groups 1A and 2A ($P < 0.001$), significantly greater than the value in group 4A ($P < 0.001$) but not significantly different from that in group 3A ($P > 0.05$). Peak hyperemic response in class B was significantly greater than the hyperemic response in groups 1A and 2A ($P < 0.05$), significantly less than that in group 4A ($P < 0.001$) but not significantly different from that in group 3A ($P > 0.05$).

The correlation between hyperemic response and poststenotic pressure ratio in progressive coronary sclerosis is shown in Figure 2. Regardless of the degree of stenosis or the presence of collateral channels, all data were used except those from the patients with experimental acute occlusion (group 4A). The relation can be described by a linear regression with a correlation coefficient of 0.85 ($P < 0.001$).

Frequency of myocardial infarction and extent of local left ventricular wall motion: Electrocardiographic evidence of previous myocardial infarction was found in 31 percent of all patients. The frequency of left ventricular dyskinesia (hypokinesia or akinesia in the area supplied by the stenotic coronary artery) increased with the severity of coronary obstruction. In group 1A 45 percent of the wall segments were dyskinetic, in group 2A 52 percent and in group 3A 57 percent. In class B 63 percent of the wall segments were dyskinetic.

General hemodynamics: As an estimate of myocardial oxygen consumption, pressure-rate product, calculated by multiplying mean systemic pressure by heart rate, was determined during the period of graft flow measurements. The mean values did not differ significantly among groups ($P > 0.05$) (Table II).

Discussion

Possible limitations of the study: To evaluate the physiologic significance of coronary arterial stenosis, coronary pressure and flow data must be available; thus, such evaluation can be done in man only during aorto-coronary bypass surgery. Although direct measurements of flow with an electromagnetic flowprobe on the stenotic segment of the coronary artery itself and pressure measurements by puncture of the coronary artery distal to the lesion may damage the coronary vessels, graft flow and pressure can easily be measured without risk to the patient.[7,9,10] Indeed, in the presence of an intact anastomosis and with the graft closed, pressure in the graft distal to the occlusion reflects poststenotic coronary pressure. Closure of the graft restores the original situation immediately, and the peripheral vascular resistance decreases in proportion to the reduced poststenotic pressure. Sudden release of the graft clamp produces a hyperemic response in the graft flow. It is not known whether this positive hyperemia represents a response to ischemia or is a reflection of decreased arterial tone due to the decreased perfusion pressure. The significant relation between poststenotic pressure and postocclusion hyperemia suggests the latter. However, this linear correlation occurred because data from the group with acute occlusion were omitted; acute coronary occlusion produced disproportionately

high peak hyperemic responses by comparison with chronic coronary occlusion. This discrepancy between acute and chronic coronary occlusion in relation to the hyperemic response is probably due to the presence of coronary collateral channels after chronic occlusion and the absence of such channels in acute occlusion. On the other hand, a reduced vascular responsiveness after long-term occlusion cannot be excluded.

Although mean values for hyperemic response and poststenotic pressure differed significantly between most groups, individual data varied widely. There are many reasons for this scatter of individual data points. First, there is the problem of accurate estimation of the degree of coronary stenosis. Despite recent progress in angiographic techniques,[8] the exact evaluation of coronary narrowing remains difficult in certain cases. Therefore we did not grade stenosis precisely but classified the patients in groups with a range of 10 percent luminal narrowing. Second, we assumed that all anastomoses were of good quality. We could show that graft flow increased in all instances after injection of dipyridamole, but we could not be certain that no graft was flow-limiting at the highest flow rates. Reneman and Spencer[7] have shown that stenosis of the graft anastomosis decreases the hyperemic response.[7]

Another important consideration is that the response depends upon resting coronary flow, that is, oxygen consumption of the myocardium. We tried to assess oxygen requirements of the heart by determining pressure-rate product. Although the same method of anesthesia was used in all patients and measurements of flow and pressure were performed at approximately the same time interval after termination of bypass grafting, pressure-rate product was not always constant. Arterial perfusion pressure is known to affect hyperemic flow.[11] The variation in arterial blood pressure among patients is probably a further source of error in the exact determination of hyperemic response.

Hemodynamic significance of coronary stenosis: It is clearly observable under basal conditions that coronary stenosis in patients without angiographically visible collateral channels produces significant changes in coronary hemodynamics when stenosis is 80 percent or greater. We found that vessels with greater than 80 percent stenosis have a significant pressure gradient across the stenosis and that the hyperemic response in grafts to these vessels becomes significant. This indicates that under resting conditions a coronary lesion becomes "critical" when there is 80 percent narrowing of luminal diameter. These findings are in agreement with recent investigations[12,13] demonstrating a reduced hyperemia after intracoronary injection of contrast agent in patients with coronary stenosis of 75 percent or more. Furthermore, we found a good correlation between observed stenosis, graft flow hyperemia and poststenotic pressure. The failure of other investigators[10,14,15] to show this relation is probably due to critical differences in types of patients. These investigators did not measure coronary stenosis and they did not differentiate between cases with and without angiographically visible collateral channels.

Functional significance of coronary collateral channels: Unfortunately, angiographic methods used to study collateral circulation in man do not give quantitative information about collateral function; indeed, the estimation is subjective.[2,16–19] With our more direct approach we found that collateral vessels produce in a completely obstructed coronary artery hemodynamic changes that simulate those of a 90 percent coronary stenosis without collateral channels. However, the extent of the collateral circulation is a critical point in our data interpretation. Indeed, in view of the great diversity of the magnitude of collateral vessels observed angiographically, the homogeneity of response in our group with collateral vessels may be unexpected. However, good retrograde filling of the distal segment of the obstructed coronary vessel was a condition for surgery in our patients. Thus our patients were a selected group with complete occlusion and well developed collateral vessels; good retrograde filling implies good collateral development in patients with complete coronary occlusion. Patients with complete coronary obstruction and poorly opacified distal coronary segments, that is, poorly developed collateral vessels, were not selected for surgery and hence not included in our study.

Intraoperative measurements of collateral indexes in man are scarce; only a few investigators have studied retrograde flow[20] or retrograde pressure[14,15] during surgery. In patients without occlusive coronary artery disease Goldstein et al.[20] described a peripheral coronary pressure of 19 to 24 percent in contrast to 50 percent in well collateralized distal segments of diseased coronary arteries. Retrograde flow was significantly greater in the group with collateral channels. Parker et al.[14] also reported that increased retrograde flow correlates with the presence of collateral vessels on arteriography. However, none of these investigators compared coronary hemodynamics in patients with collateralized complete occlusion with the hemodynamics in patients with coronary stenosis without collateral vessels.

In summary, we found that coronary collateral vessels, although identified angiographically as significant, compensate only partially for the coronary obstruction.

References

1. **Schaper W, Flameng W, Winkler B, et al:** Quantification of collateral resistance in acute and chronic experimental coronary occlusion in the dog. Circ Res 39:371–377, 1976
2. **Hamby RI, Aintablian A, Schwartz A:** Reappraisal of the functional significance of the coronary collateral circulation. Am J Cardiol 38:305– 309, 1976
3. **Ritchie JL, Hamilton GW, Gould KL, et al:** Myocardial imaging with Indium-113m- and technetium 99m-macroaggregated albumin. New procedure for identification of stress-induced regional ischemia. Am J Cardiol 35:380–389, 1975

4. **Zaret BL, Strauss HW, Martin ND, et al:** Non-invasive evaluation of myocardial perfusion with potassium-43. Study of patients at rest, exercise and during angina pectoris. N Engl J Med 288: 809–812, 1973
5. **Strauss HW, Hamilton K, Laugan JK, et al:** Thallium-201 for myocardial imaging: relation of thallium-201 to regional myocardial perfusion. Circulation 51:641–645, 1975
6. **Bloor CM, Roberts LE:** Effect of intravascular isotope content on the isotope determination of coronary collateral blood flow. Circ Res 16:537–542, 1965
7. **Reneman RS, Spencer MP:** The use of diastolic reactive hyperemia to evaluate the coronary vascular system. Ann Thorac Surg 13: 477–487, 1972
8. **Brown BG, Bolson E, Frimer M, et al:** Quantitative coronary arteriography. Circulation 55:329–337, 1977
9. **Kreulen TH, Kirk ES, Gorlin R, et al:** Coronary artery bypass surgery: assessment of revascularization by determination of blood flow and myocardial mass. Am J Cardiol 34:129–135, 1974
10. **Bittar N, Kroncke GM, Dacoumos GC, et al:** Vein graft flow and reactive hyperemia in the human heart. J Thorac Cardiovasc Surg 64:855–860, 1972
11. **Rodbard S, Kikuchi Y:** Arterial stenosis, pressure and flow. J Thorac Cardiovasc Surg 71: 891–898, 1976
12. **Gould KL, Lipscomb K, Hamilton GW:** Physiologic basis for assessing critical coronary stenosis. Am J Cardiol 33:87–94, 1974
13. **Holman BL, Cohn PF, Adams DF, et al:** Regional myocardial blood flow during hyperemia induced by contrast agent in patients with coronary artery disease. Am J Cardiol 38:416–421, 1976
14. **Parker FB, Neville JF, Hanson EL, et al:** Retrograde and antegrade pressures and flows in preinfarction syndrome (abstr). Circulation 49, 50: Suppl II:II-122–II-126, 1974
15. **Smith SC, Gorlin R, Herman MV, et al:** Myocardial blood flow in man: effects of coronary collateral circulation and coronary artery bypass surgery. J Clin Invest 51: 2556–2565, 1972
16. **Lavine P, Filip Z, Najmi M, et al:** Clinical and hemodynamic evaluation of coronary collateral vessels in coronary artery disease. Am Heart J 87:343–349, 1974
17. **Helfant RH, Vokonas PS, Gorlin R:** Functional importance of the human coronary collateral circulation. N Engl J Med 284:1277–1281, 1971
18. **Levin DC:** Pathways and functional significance of the coronary collateral circulation. Circulation 50:831–837, 1974
19. **Carroll RJ, Verani MS, Falsetti HL:** The effect of collateral circulation on segmental left ventricular contraction. Circulation 50: 709–713, 1974
20. **Goldstein RE, Michaelis LL, Morrow AG, et al:** Coronary collateral function in patients without occlusive coronary artery disease. Circulation 51:118–125, 1975

Effect of Coronary Stenosis on Myocardial Function, Ultrastructure and Aortocoronary Bypass Graft Hemodynamics

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The relation between different degrees of stenosis of the left anterior descending coronary artery and total and regional left ventricular function, myocardial ultrastructure, fibrotic content of the myocardium and hemodynamics of graft flow was studied in 70 patients with coronary artery disease. Patients with arteriographically visible collateral supply to the obstructed vessel were excluded. The degree of stenosis (quantitative measurement of luminal obstruction) and total and regional left ventricular function were measured angiographically. Regional contractile reserve was determined from postextrasystolic angiograms. Ultrastructure and fibrotic content of the myocardium (morphometry) were determined from biopsy material taken at the time of bypass surgery from the area perfused by the left anterior descending artery. Graft flow to this artery was measured under basal conditions and after release of a 30 second graft occlusion (hyperemic response). Five groups were formed: I, no stenosis; II, stenosis of 50 to 79 percent; III, of 80 to 89 percent; IV, of 90 to 99 percent; and V, 100 percent occlusion. Patients in group II had normal values for ejection fraction, regional function and reserve, normal ultrastructure, a small degree of fibrosis and no hyperemic response after release of graft occlusion. Patients in group III had similar findings except for a significant hyperemic response. Patients in group IV had moderate depression of ejection fraction, regional function and reserve, moderate ultrastructural alterations, increased myocardial fibrosis and a high hyperemic response. Patients in group V had a severely impaired ejection fraction, absent regional function and reserve, severe cell alterations and extensive scar formation.

Thus, a clear sequence of events occurs with progression of coronary stenosis: until 79 percent stenosis no significant reduction of mechanical function and myocardial structure occurs. With 80 to 89 percent stenosis, poststenotic vasodilation fully compensates for the stenosis as documented by normal mechanical function and normal myocardial structure. At 90 to 99 percent stenosis, vasodilatory compensation is inadequate: Regional function decreases, degenerative ultrastructural alterations appear and the fibrotic content of the myocardium increases. With complete occlusion, compensation is ineffective, and severe loss of function and extensive scars develop.

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Regional myocardial dysfunction is a well known consequence of obstructive coronary artery disease. In general, the frequency of ventricular asynergy of contraction is thought to increase with the severity of vascular disease, but hemodynamic abnormalities do not always correlate with the extent of vessel disease.[1] Cohn et al.,[2] in a consecutive series of 100 patients, found no significant difference in ejection fraction or asynergy among patients with one, two and three vessel disease, although hemodynamic abnormalities were more frequent in the patients with more extensive vascular lesions. They concluded that abnormal dynamic

morphology and hemodynamics may bear no direct relation to the extent of vessel involvement. Several other studies[3–5] also failed to establish a clear-cut relation between the severity of coronary lesions and the hemodynamic and ventriculographic abnormalities, thus suggesting that the relation between coronary and myocardial lesions may not be simple. When regional dysfunction is severe, overt depression of overall cardiac function with recognizable clinical manifestations occurs. If regional dysfunction is less extensive, the clinical and mechanical abnormalities are more subtle. However, these changes are important because they may represent a stage in which aortocoronary bypass surgery can considerably improve regional myocardial function.[6,7] Furthermore, these subtle changes may precede the more severe stage of coronary artery disease that causes extensive loss of myocardium by infarction.[8]

Recently, a method of quantitative coronary arteriography was introduced that allows one to measure the vascular lesion with great accuracy.[9] This study was undertaken to reevaluate the effect of coronary stenosis, as assessed with quantitative coronary arteriography, on regional wall motion and myocardial structure. In addition, hemodynamic data on the aortocoronary bypass graft were obtained during open heart surgery to estimate the hemodynamic effect of vessel stenosis on the poststenotic vascular bed in the same patient group. Because the effect of coronary collateral vessels on function and structure of the myocardium in severe obstructive coronary artery disease remains unclear,[10–12] we excluded all patients with arteriographically visible collateral supply to the poststenotic vessel segment.

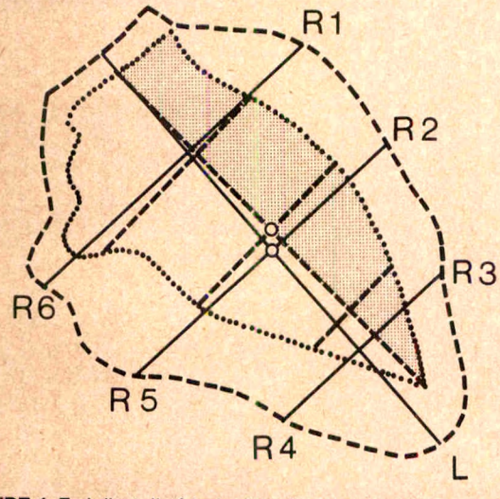

FIGURE 1. End-diastolic **(dashed line)** and end-systolic **(dotted line)** ventriculographic silhouettes of the left ventricle. The long axis (mid aortic root to apex) for end-diastole **(solid line)** and end-systole **(dashed line)** is depicted. The **open circles** represent the "mid point" of each silhouette. The percent shortening of each hemiaxis (R_1 to R_6 and L) is calculated as end-diastolic minus end-systolic hemiaxis, divided by end-diastolic hemiaxis times 100 percent. The anterior wall is marked by the **shaded area.** The area perfused by the anterior descending branch of the left coronary artery was taken as the average of $R_2 + R_3 + L$.

Methods

Patients: Initially we studied 92 consecutive surgical patients with obstructive coronary artery disease who underwent aortocoronary bypass surgery or aneurysmectomy. The patients (6 women, 86 men) were 35 to 64 years old. From this group we excluded 22 patients who had one or more of the following: significant (more than 50 percent luminal narrowing) obstruction of the circumflex branch of the left coronary artery (18 patients), significant obstruction of the left main stem (2 patients), peripheral obstruction of the anterior descending branch of the left coronary artery (1 patient) or collateral supply to the anterior descending branch (17 patients). Criteria for the presence of coronary collateral vessels, either intracoronary or intercoronary anastomosis, required arteriographic visualization of the left anterior descending branch distal to the coronary obstruction. These criteria are similar to those of Hamby et al.[12] The remaining 70 patients had significant proximal obstructive disease of the left anterior descending branch, and 37 of them had additional disease of the right coronary artery. Twenty-nine patients had a typical history and electrocardiographic changes (abnormal Q waves) suggestive of old myocardial infarction (anterior in 23, inferior in 6). All patients had ventriculographic and coronary arteriographic studies within 6 weeks before surgery because of chronic angina or previous myocardial infarction with symptoms of congestive heart failure or rhythm disturbances. No patient studied had an acute event between cardiac catheterization and aortocoronary bypass operation. Twenty-two patients who had no signs of coronary, myocardial or valvular heart disease served as controls for angiographic measurements.

Catheterization study: All patients were studied during normal sinus rhythm. No patient had chest pain during cardiac catheterization. No premedication was used. Administration of nitrates and beta receptor blocking drugs was discontinued at least 3 days before the study. Left heart catheterization was performed with the retrograde technique. After measurement of left ventricular pressure, biplane left ventricular angiography was performed in the 30° right anterior oblique projection after injection of 50 ml Urografin-76®. Thereafter, coronary arteriography was carried out with the Judkins technique[13] using 35 mm film taken at 48 frames/sec utilizing the Philips dual field 9 and 5 inch (22.9 and 12.7 cm) image intensifier system. Selective coronary injections were made in multiple projections by manual injection of 6 to 8 cc of Urografin-76. From the cineangiographic frames, silhouettes of the left ventricular cavity were drawn at end-diastole and end-systole. Ectopic cycles were eliminated.

Ventricular volumes and ejection fraction were calculated using the biplane area-length method.[14] Correction factors for magnification and pincushion effect were obtained from a grid filmed in the plane occupied by the left ventricle. The regression equation of Kasser and Kennedy[15] was used. In 15 patients without heart disease we found no significant difference between angiographically assessed stroke volume and stroke volume determined from manually checked cardiac output determinations obtained with the thermodilution technique (no. 7F Swan-Ganz thermodilution catheter coupled to a cardiac output computer [Fa. Diefenbach, Ffm.] and to a Kipp B-12 direct-writing system). Stroke volume assessed with thermodilution was 45.4 ± 10.8 ml/m^2 (mean ± standard deviation); the angiographic value was 44.8 ± 10.2 ml/m^2. These values are in close agreement with the normal data reported by others.[16]

Wall motion was measured from the frontal end-diastolic and end-systolic outlines of the left ventricle (Fig. 1). The long

axis was divided into four equal parts, and three perpendicular lines were constructed. Each hemiaxis (from the long axis to the endocardial surface) was measured, and percent shortening was determined as end-diastolic minus end-systolic hemiaxis divided by end-diastolic hemiaxis times 100 percent.[17–19] The individual values for three hemiaxes, R_2, R_3 and L, were averaged to get a representative measurement of regional motion of those areas of myocardial territory distal to obstruction of the anterior descending branch of the left coronary artery. Regional wall motion was also analyzed in postextrasystolic beats that followed a coupling interval of less than 400 msec.[20,21] The degree of coronary stenosis of the left anterior descending branch was measured using the technique of quantitative coronary arteriography, as suggested by Brown et al.[9]

Coronary arterial lesions were traced from two projected perpendicular 35 mm cineangiographic views. Magnification and distortion were corrected using the coronary catheter. The technique assumes an elliptical lumen of the vessel and calculates the percent reduction in luminal area in the stenosis. Diameters of the vessel were measured from diastolic frames. The normal lumen is calculated as the average of the normal vascular lumen proximal and distal to the stenosis. Two assessments of 14 stenoses by the same trained observer showed an average difference of 1.8 ± 2.0 (mean value ± standard deviation) percent stenosis. The single assessments by two trained observers of 18 stenoses showed an average difference of 2.8 ± 1.6 percent stenosis.

Coronary bypass surgery: All patients were operated on with use of total cardiopulmonary bypass and a disposable bubble-type oxygenator. A transmural needle biopsy specimen measuring 1.5 mm in diameter (Tru-Cut biopsy needle, Travenol Laboratories) was obtained from the center of the area perfused by the diseased anterior descending branch. The biopsy specimens were taken from the beating heart before cross-clamping of the aorta. Immediately after biopsy, the tissues were divided into a subepicardial, intramural and subendocardial sample (of about equal size) and were fixed in cacodylate-buffered 6 percent glutaraldehyde. After immersion fixation for 24 hours at 4° C the samples were rinsed in 0.1 molar cacodylate buffer with 7.5 percent sucrose during 12 hours at 4° C. After postfixation for 1 hour in 2 percent osmium tetroxide in veronal acetate buffer at pH 7.4 with 4 percent sucrose at 4° C, the tissues were dehydrated in graded series of ethanol, treated with propylene oxide and embedded in Epon-812. After polymerization, semithin sections of 1 to 2 μm thickness were prepared and stained with alkaline toluidine blue for light microscopy. Each block measured from 1 to 4 mm^2 in area.

Morphometry was carried out with the light microscope using a special grid with vertical and horizontal lines providing 121 intersections (points). According to the basic principles of morphometry,[22] counting of the number of points overlying a certain structure results in a quantitative determination of the volume of the structure under investigation in relation to the volume of the entire tissue under the square grid. The total number of points was regarded as 100 percent, and the points counted in the fibrotic area were expressed as the percent of the entire tissue within the limits of the grid. The axis of the square grid was then rotated about 45° and determination of the points was repeated.

Paired analysis of the first (x) and second (y) determinations after rotation within the same area showed no significant difference ($P > 0.05$). Regression analysis revealed the following relation of both measurements: $y = 0.54 + 0.98\,x$, correlation coefficient (r) = 0.986. After a random sampling procedure, a different area of the same section was chosen and the points overlying fibrotic tissue were counted with the grid in control position and after rotation of about 45°. Paired comparison of the first determination in the control position (x) and the second determination in the control position of a different area (y) showed no significant difference ($P > 0.05$). Regression analysis showed the following equation: $y = 3.87 + 0.93\,x$, $r = 0.922$. In this way two different areas of each section were counted twice.

Only longitudinal sections at a magnification of ×250 were evaluated, and blood vessels and perivascular interstitial cells were excluded from the fibrotic area. For each patient three

TABLE I

Relation of Degree of Coronary Stenosis to Functional and Morphologic Characteristics (mean values ± standard error of the mean)

Groups	Patients (no.)	LAD Stenosis (%)	Ejection Fraction, Normal Beat (%)	LAD wall motion: Normal beat (%)	LAD wall motion: PES Beat (%)	Fibrosis of LAD Region (%)	Patients With Myofibrillar Lysis (%)	Patients With Cell Atrophy (%)	Maximal Reactive Hyperemia of LAD Graft (%)
I	22	0	65.2 ± 1.9 (no. = 22)	39.4 ± 2.1 (no. = 22)	47.8 ± 1.9 (no. = 22)	. . .	. . .	. . .	. . .
II	6	50–79	64.8 ± 1.8 (no. = 5)	35.8 ± 2.2 (no. = 6)	45.2 ± 2.7 (no. = 5)	29.5 ± 0.7 (no. = 5)	0 (no. = 5)	0 (no. = 5)	102.3 ± 1.8 (no. = 6)
P*	. . .	. . .	NS	NS	NS	. . .	. . .	. . .	. . .
III	24	80–89	62.4 ± 2.1 (no. =8)	34.0 ± 1.6 (no. =23)	43.0 ± 2.2 (no. = 11)	27.6 ± 1.9 (no. = 15)	40 (no. = 15)	0 (no. = 15	125.1 ± 4-8 (no. = 22)
P*	. . .	. . .	NS	NS	NS	NS	. . .	. . .	<0.001
IV	34	90–99	54.9 ± 2.5 (no. = 25)	22.8 ± 2.2 (no. = 32)	26.9 ± 2.7 (no. = 19)	41.5 ± 3.8 (no. = 16)	38 (no. = 16)	31 (no. = 16)	159.5 ± 11.4 (no. = 27)
P*	. . .	. . .	<0.05	<0.001	<0.001	<0.01	. . .	. . .	<0.01
V	6	100	40.0 ± 2.1 (no. = 6)	4.0 ± 1.5 (no. = 6)	6.4 ± 1.7 (no. = 5)	79.0 ± 2.5 (no. = 5)	0 (no. = 5)	100 (no. = 5)	. . .
P*	. . .	. . .	<0.001	<0.001	<0.001	<0.001	. . .	. . .	. . .

P* = probability value, comparison with preceding group.
LAD = anterior descending branch of the left coronary artery; NS = not significant; PES = postextrasystolic.

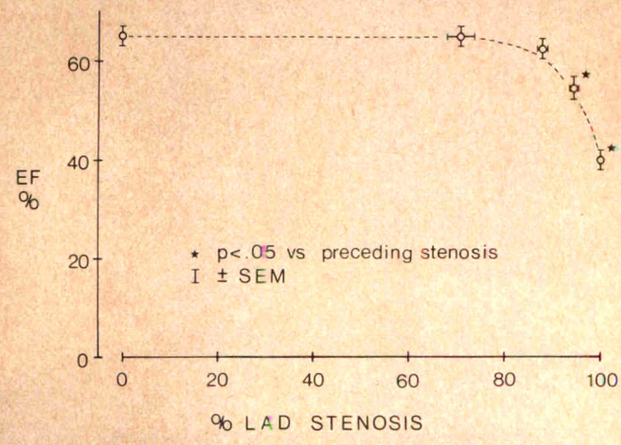

FIGURE 2. Reduction of ejection fraction (EF) with increasing severity of stenosis of the left anterior descending coronary artery (LAD) in isolated disease of this artery without any collateral supply. When stenosis exceeds 80 percent of luminal diameter, ejection fraction decreases sharply. p = probability; SEM = standard error of the mean.

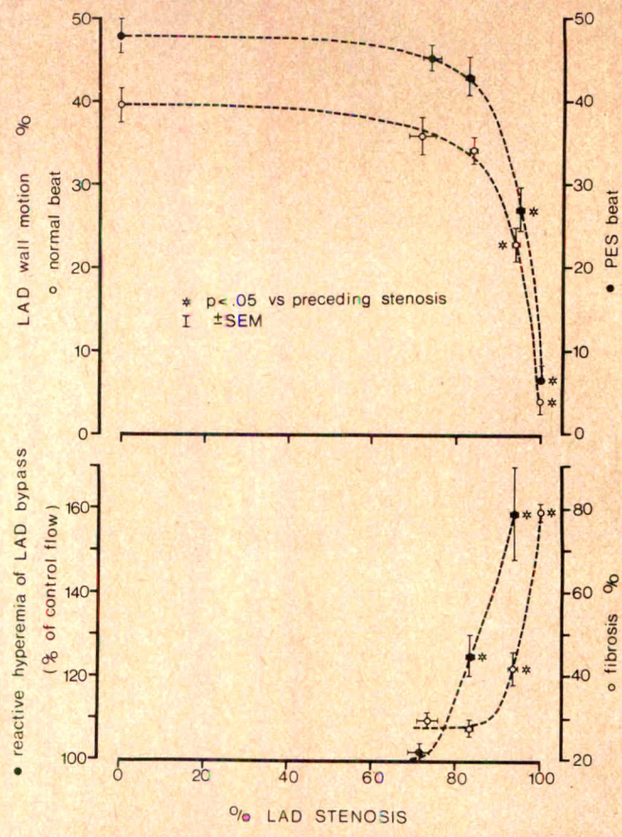

FIGURE 3. Reduction of wall motion of the area perfused by the left anterior descending coronary artery (LAD) with increasing severity of stenosis **(upper panel).** With stenosis exceeding 80 percent, a sharp decrease in wall motion develops during normal **(open circles)** and postextrasystolic (PES, **closed circles)** beats. The **lower panel** shows the reactive hyperemic response of the bypass graft to the left anterior descending artery after 30 seconds of occlusion of the graft. Abbreviations as in Figure 2.

tissue samples and from each sample two sections were counted. For electron microscopic examination thin sections were cut with an LKB Ultratome III ultramicrotome, mounted on uncoated copper grids, stained with saturated aqueous uranyl acetate and lead citrate and examined with an electron microscope (Philips 300).

Distal coronary arterial-venous anastomoses were performed using cardioplegic arrest. Measurements of aorto-coronary bypass flow (Statham E.M. flowmeter, Fa. Hellige direct-writing system) were obtained after the patients had been taken off cardiopulmonary bypass and the cannulas removed and when heart rate and arterial pressure had stabilized, as measured using brachial arterial cannulation and Statham pressure transducer. After basal graft flow was measured, the graft was cross-clamped with a rubber-tipped forceps for 30 seconds and thereafter the hyperemic response was recorded. The maximal hyperemic response was expressed as maximal hyperemic flow divided by basal flow times 100 percent.

Results

The data for biplane ejection fraction, regional wall motion, myocardial fibrosis, myocardial ultrastructure and graft flow were grouped according to the degree of stenosis of the left anterior descending coronary artery (Table I). Group I comprised normal patients without vessel stenosis (0 percent stenosis); group II, patients with 50 to 79 percent stenosis; group III, patients with 80 to 89 percent stenosis; group IV, patients with 90 to 99 percent stenosis; and group V, patients with 100 percent obstruction (complete occlusion). Evidence of previous anterior infarction was found in none of the 6 patients in group II, in 4 of the 24 patients (17 percent) in group III, in 13 of the 34 patients (38 percent) in group IV and in 6 of the 6 patients (100 percent) in group V.

Hemodynamic data: Figure 2 shows the effect of different degrees of isolated stenosis of the left anterior descending coronary artery on ejection fraction of the left ventricle. A nonlinear relation was found: Ejection fraction remained normal until stenosis reached 80 percent. Then a steep decline occurred, reaching a mean value of 40 percent when this artery was completely occluded. There was also a nonlinear relation between degree of stenosis and the regional wall motion of the area perfused by the left anterior descending artery (Fig. 3). When stenosis reached 80 percent, there was a sharp decrease in wall motion with normal and potentiated beats. At complete occlusion, akinesia developed.

Myocardial fibrosis: The extent of interstitial myocardial fibrosis varied among patients; typical examples are shown in Figure 4, a and b. Figure 4a shows a small amount of connective tissue, whereas Figure 4b illustrates severe fibrosis and loss of myocardial muscle tissue. The degree of fibrosis was generally greater in the subendocardial tissue samples than in the subepicardial samples (46 versus 7 percent, $P < 0.01$). The relation between the degree of stenosis of the left anterior descending artery and the fibrotic content of the transmural biopsy specimen is shown in Figure 3 (lower panel, open circles). The degree of fibrosis remained unchanged between stenosis of 50 to 79 percent and 80

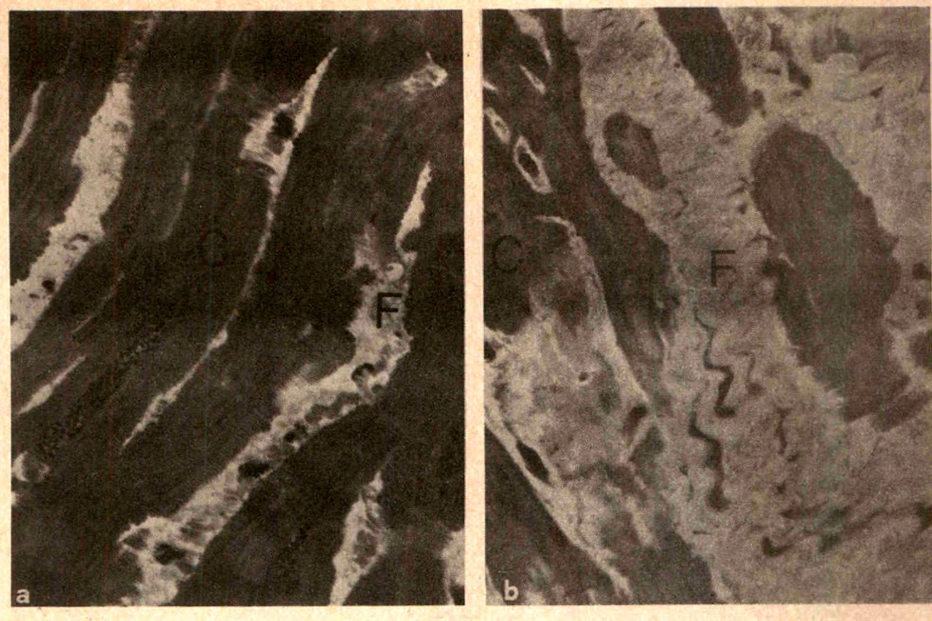

FIGURE 4. Light micrographs (×550, reduced by 25 percent). **a,** normally arranged myocardial muscle cells (C). Interstitial fibrosis (F) is mild. **b,** extensive scar tissue formation (F). Only a few myocardial muscle cells are seen.

to 89 percent but showed a sharp and significant increase when stenosis exceeded 90 percent. When the artery was completely occluded, the level of fibrous tissue reached 80 percent.

Ultrastructural findings: Electron microscopy showed ultrastructural cell abnormalities predominantly in groups IV and V; they occurred only rarely in group III and not at all in group II (Table I). These abnormalities consisted of (1) disorganization and loss of contractile elements; (2) abnormalities of Z band material; (3) alterations of mitochondria, sarcoplasmic reticulum, lysosomes and ribosomes; and (4) cell atrophy. Normal ultrastructural appearance of myocardium was found in patients in group II. The sarcomeres were normally arranged and there was only a small degree of fibrosis. Myofibrillar lysis was found in patients in groups III and IV (Fig. 5). When myofibrillar lysis was severe, "empty cells" could be seen on light microscopy (Fig. 5a). These cells showed marginally arranged myofibrils of reduced thickness but regular arrangement, whereas the areas devoid of contractile material were filled with glycogen, increased masses of sarcoplasmic reticulum, cytoskeletal filaments and few mitochondria (Fig. 5b). The loss of myofibrils was accompanied by abnormal formation of Z band material in streaming and clumping patterns (Fig. 5c). The destruction of contractile material more often involved thick than thin filaments. A more advanced stage of cell degeneration was found in patients in groups IV and V: Destruction of all cell organelles was often seen, resulting in entirely atrophic cells (Fig. 6).

Absolute objective quantification of ultrastructural changes in myocardial cells is not impossible with our technique, but some qualitative evaluation can be obtained. We accepted degenerative changes of the myocardium as significant when they were found in the majority of tissue samples. No ultrastructural changes were evident in patients in group II. Myofibrillar lysis was found in 40 percent of patients in group III, but there were no atrophic cells in this group. Myofibrillar lysis occurred in 38 percent and cell atrophy in 31 percent of patients in group IV. Only 31 percent of patients in this group had normal ultrastructure. Atrophic cells were evident in all patients in group V.

Aortocoronary bypass hemodynamics: Original tracings of aortic pressure, the electrocardiogram and graft flow are shown in Figure 7. In the presence of 71 percent stenosis, no significant hyperemic response was found, whereas in patients with 94 percent stenosis a high hyperemic response occurred after release of graft occlusion. The mean values for all patients are shown in Figure 3, lower panel. In group II no hyperemic response was found. In group III a significant hyperemic response occurred, whereas wall motion and extent of fibrosis remained unchanged from findings in group II. In group IV a high hyperemic response existed, wall motion decreased and the extent of fibrosis began to increase. Because the patients with complete coronary occlusion (group V) underwent aneurysmectomy rather than bypass grafting, no graft flow data were obtained in this group. In group II, heart rate during graft flow measurements was 89 ± 7 beats/min (mean ± standard error of the mean) and mean systemic pressure was 100 ± 8 mm Hg; in group III, heart rate was 88 ± 4 beats/min and mean systemic pressure 102 ± 4 mm Hg, and in group IV the respective values were 89 ± 3 beats/min and 100 ± 4 mm Hg. No significant differences between groups were found ($P > 0.05$). Basal flows in the graft to the left anterior descending coronary artery in groups II, III and IV were 79.7 ± 7.7, 79.4 ± 9.1 and 65.4 ± 7.1 ml/min, respectively, and were not different from each other ($P > 0.05$).

Discussion

Possible limitations of study: This study attempted to correlate the degree of coronary stenosis with the consequences for the poststenotic myocardium as evaluated from angiographic and histologic studies and graft hemodynamic measurements. Luminal obstruction of coronary stenosis was determined using the technique introduced by Brown et al.[9] This technique assumes that the coronary artery and the stenosis have an elliptical vessel cross section and calculates the percent luminal obstruction from paired perpendicular angiographic views that are not filmed simultaneously. Frame pairs are selected from different coronary arterial

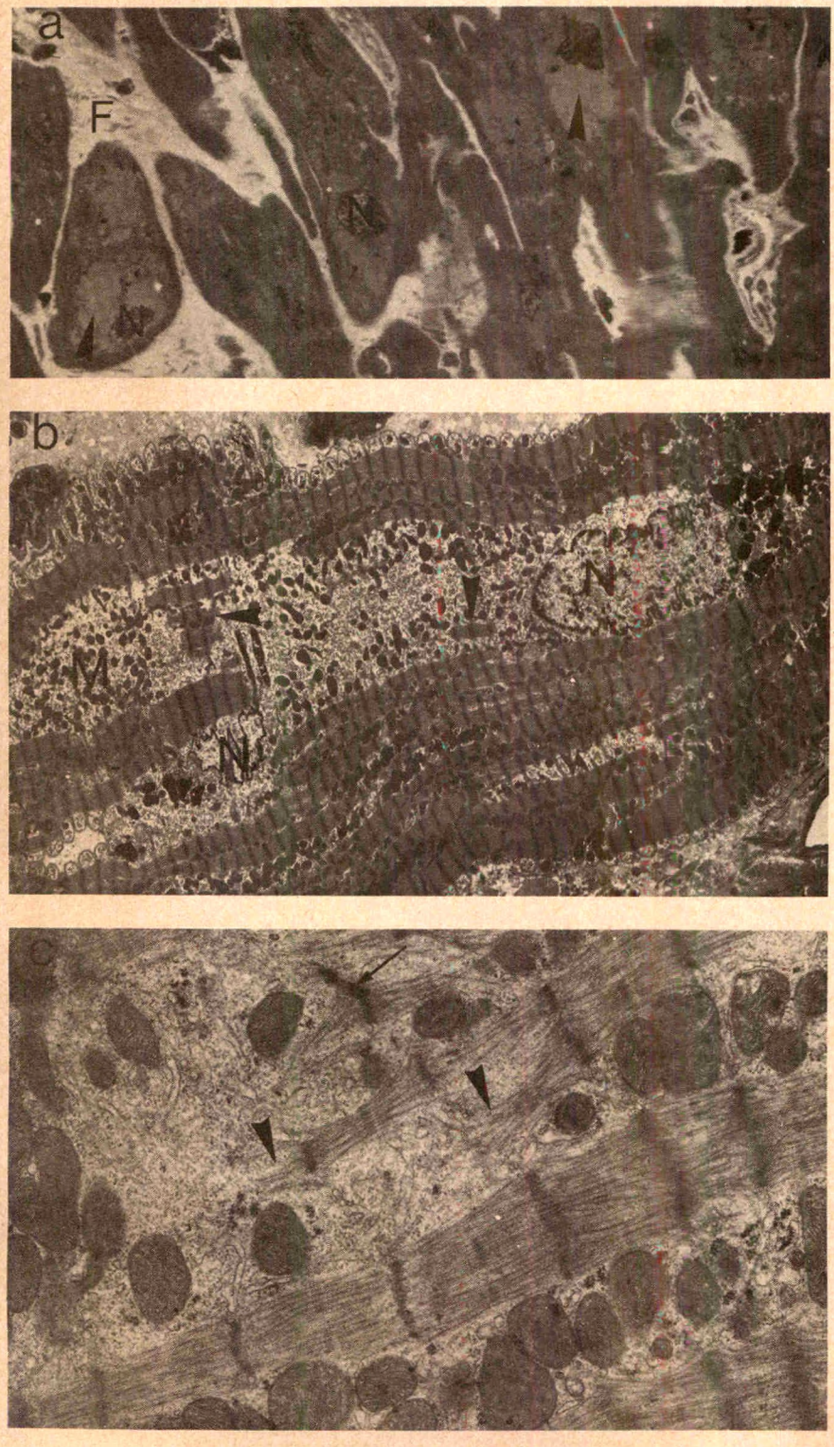

FIGURE 5. Groups III and IV. **a,** light micrograph (×650, reduced by 25 percent) of myocardial cells showing myofibrillar lysis. The interstitial fibrosis (F) is mild, but the cells show large areas free of myofibrils **(arrowheads).** The sarcomeres are marginally arranged; around the nuclei (N) palely staining areas are seen. **b,** electron micrograph (×2,400, reduced by 25 percent) of a myocyte with moderate loss of contractile material (myofibrillar lysis). Bundles of myofibrils are arranged marginally. The center of the cell is devoid of contractile material and contains mitochondria (M), the nucleus (N) and ground substance. Fragments of sarcomeric units are seen **(arrowheads). c,** electron micrograph (×20,000, reduced by 25 percent) of a part of a myocardial cell exhibiting myofibrillar lysis. The bundles of myofibrils are thinned and irregularly arranged. The Z bands show focal widening **(arrow).** Some thick filaments have lost their interconnections **(arrowheads).**

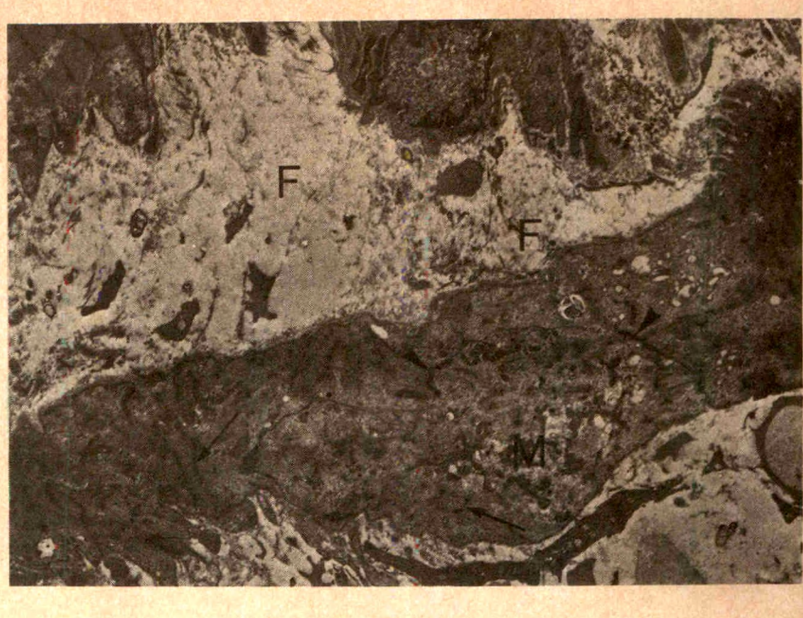

FIGURE 6. Group V. Electron micrograph (×5,600, reduced by 25 percent) of two atrophic myocardial cells in an area of extensive fibrosis (F). The cells are almost completely devoid of normally arranged contractile material and contain only small numbers of irregularly shaped mitochondria (M). The cells are connected to each other by intercalated discs **(arrowheads).** Remaining Z band material is seen within the cells **(arrows).**

injections but from the same point in the cardiac cycle, that is, end-diastole. Three main factors can interfere with correct measurement: (1) poor image quality, (2) obscuring of a lesion by an overlapping vessel, and (3) end-on viewing.[9] However, with careful attention to filming technique, we have found that more than 95 percent of lesions of the left anterior descending coronary artery can be adequately measured. We have used this technique to measure percent luminal obstruction, but not the length, the atheromatous mass or the resistance of the stenosis, and we have found good agreement among measurements. For this study only three groups of stenoses were differentiated: 50 to 79 percent, 80 to 89 percent and 90 to 99 percent; thus, erroneous measurement probably had little influence on our results. Currently used techniques using visual estimates may have considerably more error.[23]

Regional motion was assessed from normal and postextrasystolic beats. Postextrasystolic potentiation has been proposed to be useful in evaluating residual myocardial function in areas that are asynergic during normal beats.[21] The anterior wall motion in postextrasystolic beats represents the maximal contractile power of this region.

The transmural biopsy technique used in our study was previously performed by Stinson et al.[24] in patients with coronary artery disease. They found the method accurate when the data were compared with electrocardiographic and ventriculographic findings. We believe that the sampling error is small when biopsy is

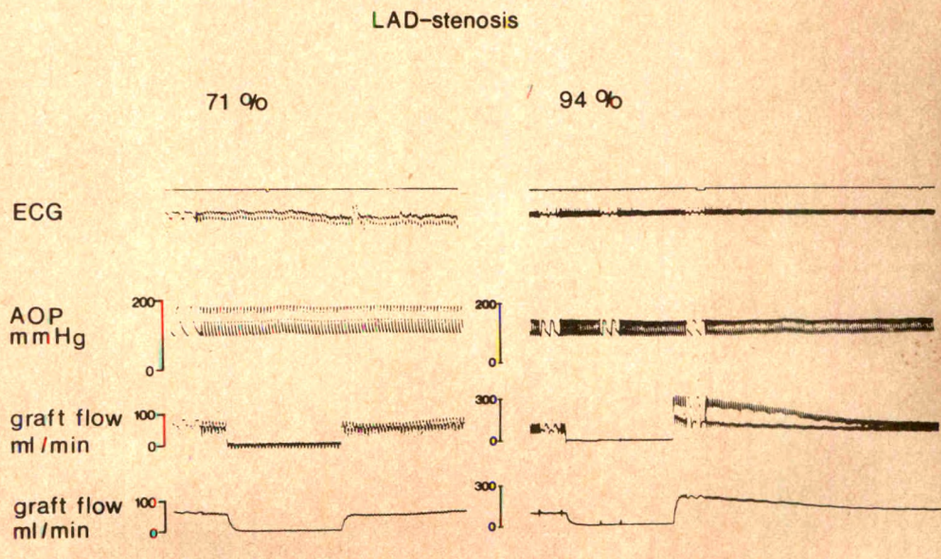

FIGURE 7. Original tracings of electrocardiogram (ECG), aortic pressure (AOP), phasic and mean graft flow to the left anterior descending coronary artery (LAD) in two patients. The **left panel** shows tracings from a patient with 71 percent stenosis (group II), the **right panel** shows tracings of a patient with 94 percent stenosis (group IV). No hyperemic response was seen in the former in contrast to the latter. Mean resting flow was 73 ml/min in the patient with 71 percent stenosis and 90 ml/min in the one with 94 percent stenosis.

performed after localization of the perfusion area of the diseased area. We evaluated the anterior region of the left ventricle, rather than the anteroapical region evaluated by Stinson et al.[24] We find the technique safe because it is performed under direct vision.

Consequences of different degrees of coronary stenosis: We evaluated graft flow at rest and after 30 seconds of graft occlusion. Graft flows were measured when blood pressure and heart rate had reached normal levels. Several studies have used graft flow measurements to evaluate the potential of coronary bypass grafts to increase blood flow to the myocardium supplied by obstructed arteries.[25,26] The significance of a hyperemic response is not fully understood. Kreulen et al.[26] found that the hyperemic response was correlated with the pressure gradient of the stenosis, that is, the severity of stenosis. However, it cannot be entirely ruled out that a positive hyperemic response represents ischemia to some extent. Reneman and Spencer[27] have shown that stenosis of graft anastomosis will decrease the hyperemic response. Such a mechanism seems unlikely in the majority of cases, as demonstrated by the identical graft flow values in groups II, III and IV. Narrowing of the distal coronary artery could have produced a similar reaction, but we studied no patient with peripheral stenosis.

Poststenotic vasodilation was not found in patients with 50 to 79 percent stenosis (no hyperemic response). A significant hyperemic response could be shown in patients with 80 to 89 percent stenosis, and the compensating effect of vasodilation was documented by a normal wall motion and regional reserve by the small degree of fibrosis and a normal ultrastructure in most cases. In patients with 90 to 99 percent stenosis the poststenotic vasodilation was associated with a decrease in mechanical function and an increase of fibrosis and is therefore indicative of myocardial ischemia.

Regional function and reserve and overall ventricular function were related nonlinearly to the severity of vessel obstruction when cases with arteriographically visible collateral vessels were excluded. One difficulty in evaluating collateral vessels is that the resolving power of arteriographic equipment limits identification to vessels with a diameter of 100 μm or more.[12] It is therefore not entirely ruled out that in some cases collateral vessels of smaller diameter may have existed but were not visualized arteriographically. Whether this type of collateral has any significance remains to be determined.

Our results show that regional contractile reserve decreased when myocardial fibrosis increased. We found greater amounts of connective tissue in the subendocardium than in the subepicardium, thus providing direct evidence that the subendocardium is more vulnerable than the subepicardium in patients with coronary artery disease. Our results are supported by careful postmortem studies[28,29] that established a close relation between wall motion abnormalities and myocardial fibrosis within discrete myocardial segments.

The most severe cell changes (*atrophic cells*) were found in group V; mild changes occurred in group IV. The cell changes were generally found when fibrotic content was moderately increased, but a significant number of patients had cell alterations without increased amount of fibrosis (group III). Obviously lysis of myofibrils precedes cell atrophy. Furthermore, when the cell structure is severely impaired, scar formation progresses. The lysis of myofibrils was associated with moderate contractile dysfunction (hypokinesia). We therefore suggest that the moderate cell alterations described (lysis of myofibrils) represent the morphologic correlate of hypokinesia. We believe that these alterations may be at least partially reversible when blood flow reduction is corrected by aortocoronary bypass grafting. This hypothesis is supported by the finding that the hypokinetic state often reverts to normal after restoration of blood flow.

In summary, our results established a nonlinear relation between the degree of coronary stenosis and poststenotic characteristics of the myocardium in human patients. With progression of stenosis up to 89 percent of luminal diameter, no significant reduction of mechanical function and myocardial structure was found. Above this level, an abrupt decrease in poststenotic motion and contractile reserve and a sharp increase in the fibrotic content of the myocardium occurred. Typical ultrastructural alterations preceded the stage of severe scar formation when coronary stenosis became more severe. These findings suggest that severe coronary lesions cause sequential changes in the morphologic features and function of the poststenotic myocardium and in themselves are an indication for operation.

References

1. **Helfant RH, Kemp HG, Gorlin R:** Coronary atherosclerosis, coronary collaterals, and their relation to cardiac function. Ann Intern Med 73:189–193, 1970
2. **Cohn PF, Herman MV, Gorlin R:** Ventricular dysfunction in coronary artery disease. Am J Cardiol 33:307–310, 1974
3. **Gorlin R:** Coronary Artery Disease. Philadelphia, WB Saunders, 1976, p 116–148
4. **Schönbeck M, Rutishauser W, Krayenbühl HP, et al:** Kineangiografische linksventrikuläre Dimensionsanalyse bei Normalen und bei Patienten mit einer koronaren Herzkrankheit. Z Kardiol 64:221–238, 1975
5. **Chatterjee K, Saccor M, Sutton GC, et al:** Angiographic assessment of left ventricular function in patients with ischaemic heart disease without clinical heart failure. Br Heart J 33:559–564, 1971
6. **Bourassa MG, Lesperance J, Campeau, L, et al:** Fate of left ventricular contraction following aortocoronary venous grafts. Early and late postoperative modifications. Circulation 46:724–730, 1972
7. **Chatterjee K, Matloff JM, Swan HJC, et al:** Abnormal regional metabolism and mechanical function in patients with ischemic heart disease. Improvement after successful regional revascularization by aortocoronary bypass. Circulation 52:309–399, 1975

8. **Kimbiris D, Lavine P, van den Broek H, et al:** Devolutionary pattern of coronary atherosclerosis in patients with angina pectoris. Coronary arteriographic studies. Am J Cardiol 33:7–11, 1974
9. **Brown G, Bolson E, Frimmer M, et al:** Quantitative coronary arteriography: estimation of dimensions, hemodynamic resistance and atheroma mass of coronary artery lesions using the arteriogram and digital computation. Circulation 55:329–337, 1977
10. **Caroll RJ, Verani MS, Falsetti HL:** The effect of collateral circulation on segmental left ventricular contraction. Circulation 50: 709–713, 1974
11. **McGregor M:** The coronary collateral circulation. A significant compensatory mechanism or a functionless quirk of nature. Circulation 52:529–530, 1975
12. **Hamby RI, Aintablian A, Schwartz A:** Reappraisal of the functional significance of the coronary collateral circulation. Am J Cardiol 38:305–309, 1976
13. **Judkins MP:** Percutaneous transfemoral selective coronary arteriography. Radiol Clin North Am 6:467–492, 1968
14. **Cohn PF, Gorlin R, Adams DF, et al:** Comparison of biplane and single plane left ventriculograms in patients with coronary artery disease. Am J Cardiol 33:1–6, 1974
15. **Kasser IS, Kennedy JW:** Measurement of left ventricular volumes in man by single-plane cineangiography. Invest Radiol 4:83–90, 1969
16. **Kennedy JW, Baxley WA, Figley MM, et al:** Quantitative angiography. I. The normal left ventricle in man. Circulation 34:272–279, 1966
17. **Herman MV, Gorlin R:** Implications of left ventricular asynergy. Am J Cardiol 23:538–547, 1969
18. **Sniderman AD, Marpole D, Fallen EL:** Regional contractile patterns in the normal and ischemic left ventricle in man. Am J Cardiol 31:484–489, 1973
19. **Leighton RF, Wilt SM, Lewis RP:** Detection of hypokinesis by a quantitative analysis of left ventricular cineangiograms. Circulation 50:121–127, 1974
20. **Hamby RI, Aintablian A, Wisoff WG, et al:** Response of the left ventricle in coronary artery disease to postextrasystolic potentiation. Circulation 51:428–435, 1974
21. **Dyke SH, Cohn PF, Gorlin R, et al:** Detection of residual myocardial function in coronary artery disease using post-extra systolic potentiation. Circulation 50:694–699, 1974
22. **Weibel ER, Elias H:** Quantitative Methods in Morphology. Berlin, Springer Verlag, 1967, p 87–148
23. **Detre KM, Wright E, Murphy ML, et al:** Observer agreement in evaluating coronary angiograms. Circulation 52:979–986, 1975
24. **Stinson EB, Billingham ME:** Correlative studies of regional left ventricular histology and contractile function. Am J Cardiol 39: 378–383, 1977
25. **Greenfield JC, Rembert JC, Young WG, et al:** Studies of blood flow in aorta-to-coronary venous bypass grafts in man. J Clin Invest 51:2724–2735, 1972
26. **Kreulen TH, Kirk ES, Gorlin R, et al:** Coronary artery bypass surgery: assessment of revascularization by determination of blood flow and myocardial mass. Am J Cardiol 34:129–135, 1974
27. **Reneman RS, Spencer MD:** The use of diastolic reactive hyperemia to evaluate the coronary vascular system. Ann Thorac Surg 13:477–487, 1972
28. **Starr JW, Wagner GS, Hackel DB:** Pathologic significance of arteriographic coronary artery lesions and segmental ventricular contraction abnormalities (abstr). Circulation 49, 50: Suppl III:III-150, 1974
29. **Ideker R, Behar V, Starr J, et al:** Evaluation of asynergy as an indicator of myocardial fibrosis (abstr). Circulation 53, 54: Suppl II: II-40, 1976

Risk Stratification After Acute Myocardial Infarction

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One hundred patients admitted to the hospital with acute myocardial infarction who lived 10 days and agreed to enroll were studied. Data from the history, hospital course and a 24 hour Holter electrocardiographic recording were related to cardiac mortality in the 6 months after enrollment. Fifteen cardiac deaths occurred during this period; 12 of these were sudden. The univariates with the strongest association with mortality were (in descending order): blood urea nitrogen level, serum creatinine level, serum uric acid level, enlarged heart 2 weeks after infarction, ventricular tachycardia 2 weeks after infarction, peak creatine kinase level and left ventricular failure in the coronary care unit. The odds of dying if one of these factors was present rather than absent ranged from 3.6 to 11.5. Groups with two or three of these univariates had up to 20 times the odds of dying in 6 months. A period of greatly enhanced risk for cardiac death persists for about 6 months after acute myocardial infarction. Relatively simple clinical variables can identify the groups at highest and lowest risk. This information is useful for designing management strategies.

Of people who survive the first 24 hours of acute myocardial infarction, about 6 percent die of cardiac causes in the following month, and about 8 percent die in the subsequent 5 months.[1] After about 6 months, the incidence rate of cardiac death decreases to 3 to 4 percent per year, which is comparable with the cardiac death rate for patients with chronic ischemic heart disease.[1,2] Because the excess influence on mortality exerted by infarction is almost dissipated by 6 months, any therapeutic intervention, such as antiarrhythmic prophylaxis or a cardiac surgical procedure, designed to alter favorably the posthospital course of high risk patients should be applied early after acute myocardial infarction. Also, it is reasonable to discontinue some interventions about 6 months after hospital discharge. Because prophylactic intervention may carry its own morbidity and mortality, the prospect of intervention lends considerable impetus to the effort to identify patients who are at high risk of cardiac death within the first 6 months after acute myocardial infarction. In addition, it would be useful to define a very low risk group in order to spare these patients the costs and risks of unnecessary tests and therapy, as well as the anxiety of an ill defined prognosis.

Several studies have used clinical or demographic data and specific laboratory methods including prolonged Holter electrocardiographic recordings to delineate high and low risk groups.[1–11] Similarly, the purpose of our cohort study was to find a set of criteria, using simple clinical and laboratory data, that would separate our patient population into a group with a high risk and another with a significantly lower risk of dying within 6 months after acute myocardial infarction. We were successful in identifying high risk groups using relatively simple variables. Variables reflecting the extent of acute myocardial infarction, cardiac arrhythmia and left ventricular dysfunction have the strongest

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association with cardiac death in the 6 months after recovery from acute myocardial infarction.

Methods

Protocol: We planned to study 100 consecutive patients who had acute myocardial infarction. After the study began, the charts of all patients hospitalized for suspected acute myocardial infarction were reviewed, and the diagnosis of acute myocardial infarction was made on the basis of either (1) a history of typical chest pain and typical evolution of Q waves diagnostic of acute infarction, or (2) S-T and T wave changes compatible with acute myocardial infarction and diagnostic elevation of the serum myocardial creatine kinase level. The study was discussed with eligible patients on the 9th hospital day. Patients gave informed consent, usually on the 10th day. Data from the history, physical examination and hospital course were recorded on forms, coded and logged onto digital computer files. About 2 weeks after admission, 24 continuous hours of electrocardiogram were recorded on an Avionics model 400 recorder; all patients were ambulatory during the recording. The study was terminated when 100 of the 24 hour recordings were successfully obtained.

The patient population: From June 12, 1974 to January 4, 1975, 137 patients were treated for acute myocardial infarction in the Presbyterian Hospital. Twenty of the 137 patients died before the 9th hospital day, and 2 patients were discharged before the anticipated enrollment date, leaving 115 study candidates. Twelve of these 115 candidates refused the study and three technical failures occurred, leaving a study group of 100 patients. The 15 nonparticipants did not differ from participants with respect to age, sex distribution, presence of infarction as assessed from Q waves, peak creatine kinase value, complications in the coronary care unit or outcome (three cardiac deaths within 6 months).

Analysis of 24 hour electrocardiographic recording: Each 24 hour recording was printed out on Grass polygraph paper. When less than 30 ventricular premature depolarizations per hour were present, each ventricular premature depolarization was counted. When there were more than 30 ventricular premature depolarizations per hour (13 patients), the number of depolarizations on every 10th page were counted and multiplied by 10. For each ventricular premature depolarization counted, its shape was characterized and the R-V (coupling) interval and the preceding R-R and Q-T intervals were measured. Frequency of ventricular premature depolarizations was expressed as the average per hour, that is, the total count in a record divided by the number of hours processed. An R on T phenomenon was defined as an R-V/Q-T ratio of less than 1.0, where R-V is the coupling interval.

Follow-up: After hospital discharge, patients were followed up for 12 months to determine cardiac outcome. When a patient died, the next of kin or witnesses were interviewed by one of the investigators to determine the time and nature of death. History of nonfatal reinfarction was obtained from the patient or his physician, or both; the diagnosis was then confirmed with a review of hospital records.

Selection of predictive variables: Variables considered possible predictors for dividing the population into high and low risk groups included (1) coronary risk factors (a history of hypertension, smoking, hypercholesterolemia or obesity); (2) demographic and historical characteristics (age, sex, history of angina or previous myocardial infarction); (3) presence of complications in the coronary care unit (shock, systemic hypotension, arrhythmia or left ventricular failure [third sound gallop, rales and pulmonary congestion on chest roentgenography]); (4) chemical indicators of infarct size (creatine kinase [CK], lactic dehydrogenase [LDH], serum glutamic oxaloacetic transaminase [SGOT] levels); (5) site of infarction; (6) treatment (digoxin therapy in the coronary care unit, digoxin therapy at the time of the Holter recording or diuretic therapy at the time of the Holter recording); (7) enlarged heart shown in the chest roentgenogram taken just before hospital discharge; (8) blood chemistry values (blood urea nitrogen, uric acid, serum electrolytes); and (9) variables from the 24 hour electrocardiographic recording (average heart rate, frequency of ventricular premature depolarizations and the presence of certain characteristics [bigeminy, fusion beats, multiple configurations, R on T phenomenon, pairs of ventricular premature depolarizations and ventricular tachycardia] and the occurrence of supraventricular premature depolarizations).

Analysis of data: Verified data files were kept on the disk of a digital computer. Variables were tabulated, counted and analyzed statistically using the Statistical Package for the Social Sciences, version 06.[12] For continuous variables, we used the *t* test for group means to search for differences between the patients who did and did not die of cardiac causes within 6 months of infarction. Clinical variables considered possible predictors for outcome were analyzed by prognostic stratification,[13–15] a technique that divides the total study group into two subgroups based on one or more dichotomous variables in order to maximize the difference in outcome between the two subgroups. Discrete variables, such as heart failure in the coronary care unit, were noted as present or absent. Continuous variables, such as peak value of creatine kinase drawn in the coronary care unit, were optimally dichotomized with respect to 6 month cardiac mortality. After identifying the univariates that were significantly associated with 6 month cardiac mortality, we grouped these and additional variables found significant in previous studies into bi- and trivariate combinations. For bivariate combinations (Table I), patients were classified into those who had both variables (row 1) and those with neither variable or only one (row 2). Each row was subdivided into those who experienced cardiac death (column 1) and those who did not (column 2).

Trivariate combinations were evaluated by two methods. In method I (Table II), patients were partitioned into one

TABLE I

Bivariate Combinations

Characteristics Present	Cardiac Death		Total
	Present	Absent	
Both	n11	n12	n1.
None or one	n21	n22	n2.
Total	n.1	n.2	n..

TABLE II

Trivariate Combinations, Method I

Characteristics Present	Cardiac Death		Total
	Present	Absent	
All three	n11	n12	n1.
None, one or two	n21	n22	n2.
Total	n.1	n.2	n..

TABLE III

Demographic Characteristics of 100 Patients

Sex	
Male	71
Female	29
Age (yr)	
Less than 30	1
30 to 49	16
50 to 69	59
70 or more	24
Race	
White	58
Black	19
Hispanic	18
Other	5
Place of birth	
United States	50
Germany	12
Puerto Rico	10
Other Hispanic countries	9
Eastern European countries	7
Other countries	8
Not known	4
Preinfarction history	
Myocardial infarction	27
Angina pectoris	41
Left ventricular failure	12
Cigarette smoking	50
Hypertension	37
Diabetes	18
Gout	5

TABLE IV

Frequency of Variables Used in Prognostic Stratification

Continuous Variables

Variable	Partition Value*	Number of Patients: Partition Value or Above	Number of Patients: Below Partition Value	Total
BUN (mg/dl)	20	40	60	100
Creatinine (mg/dl)	1.4	19	76	95†
Uric acid (mg/dl)	7.0	22	77	99†
Peak CK in CCU (IU)	585	45	55	100
VPD	1/hr	52	48	100

Discrete Variables

Variable	Number of Patients: Variable Present	Number of Patients: Variable Absent	Total
Enlarged heart	46	54	100
Ventricular tachycardia	14	86	100
Digoxin in CCU	45	54	99†
LVF in CCU	46	54	100
R on T (R-V/Q-T < 1)	33	67	100

* Partition value = the value of each variable that was used to dichotomize the total patient group.
† Missing values.
BUN = blood urea nitrogen; CCU = coronary care unit; CK = creatine kinase; LVF = left ventricular failure; VPD = ventricular premature depolarizations.

group with all three characteristics (row 1) and a second group with either none, one or two of the characteristics (row 2). In method II, the first group comprised patients who had either two or all three characteristics (row 1), and the second group comprised patients who had none or one of the characteristics. For both methods I and II, each row was subdivided according to 6 month cardiac mortality. We used 10 univariates to establish bi- and trivariate combinations; this resulted in 45 different bivariate combinations and 120 trivariate combinations. We determined the predictive value of these bivariate and trivariate combinations for cardiac death within 6 months using prognostic stratification.[13–15]

Chi squares were calculated to determine the significance of association. The strength of association between characteristics and outcomes was estimated using the improved estimate of the odds ratio, o′.[16] Sensitivity, specificity and efficiency were calculated for each 2 × 2 table.[17]

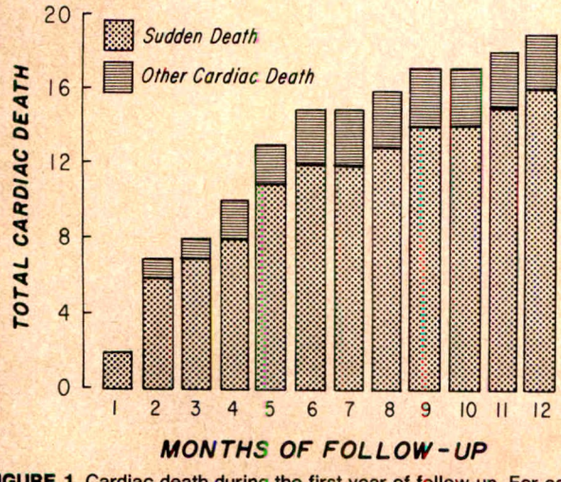

FIGURE 1. Cardiac death during the first year of follow-up. For each posthospital month, the **bar** indicates total cardiac deaths classified into sudden and other cardiac deaths. Note that 80 percent (12 of 15) of the total cumulative cardiac deaths at 6 months were sudden.

Results

There were 71 men and 29 women in the study group. The average age was 61 years (range 25 to 90). Their demographic characteristics are noted in Table III. Only half of the group were born in the United States; most of the others were born in Germany or Puerto Rico. Fifty-eight were white; the remaining 42 were of other races. About half had private insurance and half did not.

Cardiac deaths: A total of 21 deaths, including 2 of noncardiac origin, occurred within 12 months of infarction. The incidence rate of cardiac death was 15 percent in the first 6 months and 19 percent in the first 12 months (Fig. 1). The incidence rate of sudden death (within 24 hours) was 12 percent in the first 6 months and 16 percent in the first 12. Of the three nonsudden cardiac deaths, one was due to heart failure in the 4th month after acute myocardial infarction, and two were due to reinfarction with shock in the 2nd and 6th months after the index infarction. The mean age was 66 years for nonsurvivors and 60 for survivors. Because most of the cardiac deaths occurred in the initial 6 months, which is the period of excess risk related to infarction itself, we present the data for this time period

TABLE V

Prognostic Significance of Univariates for Cardiac Death Within 6 Months After Acute Myocardial Infarction

Variable	2 × 2 Table* (no. of patients)		Chi Square	Odds Ratio	Sensitivity (%)	Specificity (%)	Efficiency (%)
BUN	13	27	13.81	11.49	87	68	71
	2	58					
Creatinine	7	12	7.17	5.56	50	85	80
	7	69					
Uric acid	8	14	7.89	5.51	53	83	79
	7	70					
EH	12	34	6.68	5.33	80	60	63
	3	51					
VT	5	9	3.75	4.22	33	86	81
	10	76					
CK	11	34	4.46	3.81	73	60	62
	4	51					
Digoxin in CCU	11	34	4.30	3.74	73	60	62
	4	50					
LVF in CCU	11	35	4.09	3.64	73	58	61
	4	50					
VPD	11	41	2.29	2.74	73	52	55
	4	44					
R on T	8	25	2.31	2.69	53	71	68
	7	60					

* Column 1 = died; column 2 = lived, row 1 = present and row 2 = absent.
BUN = blood urea nitrogen 20 mg/dl or greater; CK = creatine kinase 585 IU; Creatinine = 1.4 mg/dl or greater; EH = enlarged heart on chest roentgenogram; LVF = left ventricular failure; R on T = R-V/Q-T less than 1.0; uric acid = 7 mg/dl or greater; VPD = ventricular premature depolarizations 1/hour or greater; VT = ventricular tachycardia.

only. We repeated all of the analyses using cardiac death in 12 months as the outcome; the results were substantially the same as those for 6 months.

Univariates

Eight univariates were significantly associated with cardiac death at 6 months ($P < 0.05$). Table IV lists the frequency distribution of these eight variables; frequency of ventricular premature depolarizations and the occurrence of R on T phenomenon are also listed because these two variables were significantly associated with early posthospital cardiac death in several previous studies.[3,4,7–10] Table V lists the chi square values and odds ratios for these univariates.

Coronary risk factors: A history of hypertension, diabetes mellitus, obesity, hypercholesterolemia or smoking was not significantly associated with cardiac death within 6 months.

Course in the coronary care unit: To qualify for enrollment in this study, patients had to survive 10 days after acute myocardial infarction. Therefore, patients who died in the coronary care unit of shock, hypotension or arrhythmias were not included. In our study group, the occurrence of shock, systemic hypotension or arrhythmias in the coronary care unit was not a useful predictor of cardiac death in the 6 month period after the acute myocardial infarction. There was no statistically significant difference in systolic blood pressure, pulse, peak temperature or site of infarction between survivors and nonsurvivors. However, there was a significant relation between the presence of left ventricular failure in the coronary care unit and cardiac death within 6 months ($P < 0.05$, $o' = 3.93$).

Laboratory values: Two weeks after acute myocardial infarction, the following laboratory measurements did not differ significantly between survivors and nonsurvivors: peak white blood count, hematocrit, serum potassium, serum bicarbonate and specific gravity of urine. Values for blood urea nitrogen of 20 mg/dl or greater, uric acid of 7.0 mg/dl or greater and creatinine of 1.4 mg/dl or greater were significant univariates for prognostic stratification ($P < 0.001$, 0.001, 0.005; $o' = 11.5$, 5.5, 5.6, respectively). We did not find the peak level of LDH or SGOT to be of predictive value; however, the peak creatine kinase value, dichotomized at 585 international units (IU), stratified the population into two groups with significantly different 6 month cardiac death rates ($P < 0.05$, $o' = 3.82$).

Pharmacologic therapy: Digoxin therapy in the coronary care unit was a significant predictor of cardiac death within 6 months ($P < 0.05$, $o' = 3.82$). Although the number of patients on digoxin therapy was the same as the number who experienced left ventricular failure in the coronary care unit, overlap between the two groups was not complete: 35 patients had both left ventricular failure and digoxin therapy, 45 had neither, 10 patients had left ventricular failure but no digoxin therapy and 10 were receiving digoxin but did not have left ventricular failure. Therefore, the presence of left ventricular failure and the use of digoxin therapy were not equivalent. Moreover, because the use of digoxin in

TABLE VI

Prognostic Significance of Bivariates for Cardiac Death Within 6 Months After Acute Myocardial Infarction

Variables	2 × 2 Table (no. of patients)		Chi Square	Odds Ratio	Sensitivity (%)	Specificity (%)	Efficiency (%)
BUN-CK	11	12	22.01	15.03	73	86	84
	4	73					
BUN-EH	11	14	19.06	12.60	73	84	82
	4	71					
BUN-LVF	11	15	17.76	11.62	73	82	81
	4	70					
BUN-R on T	8	8	15.18	10.33	53	91	85
	7	77					
BUN-uric acid	7	8	10.95	7.94	47	90	84
	8	76					
CK-EH	9	13	12.36	7.85	60	85	81
	6	72					
CK-LVF	11	21	11.71	7.67	73	75	75
	4	64					
BUN-VPD	9	14	11.29	7.21	60	84	80
	6	71					
R on T-EH	8	12	9.93	6.66	53	86	81
	7	73					
EH-VPD	9	18	7.88	5.33	60	79	76
	6	67					
EH-LVF	9	18	7.88	5.33	60	79	76
	6	67					

Abbreviations as in Table III.

the coronary care unit varies greatly among medical centers, we thought that this variable was not likely to be very reproducible among centers and therefore did not include it in the bivariate and trivariate combinations. Neither digoxin nor diuretic nor antiarrhythmic therapy at the time of the Holter recording was significantly related to cardiac death within 6 months.

Chest roentgenographic findings: The presence of an enlarged heart on chest X-ray examination 2 weeks after infarction was significantly associated with an increased cardiac death rate in the first 6 months ($P < 0.005$, $o' = 6.00$).

Variables from the 24 hour electrocardiographic recording: Optimal dichotomization of ventricular premature depolarization frequency was at 1 ventricular premature depolarization per hour. Patients with 1 or more ventricular premature depolarizations per hour had a higher death rate than those with a lower frequency rate of depolarizations, but the difference was not statistically significant ($P > 0.05$, $o' = 2.29$). R on T phenomenon had about the same predictive value ($o' = 2.31$). Fourteen percent of the patients had at least one episode of ventricular tachycardia (3 or more consecutive ventricular premature depolarizations). The association between ventricular tachycardia and mortality within 6 months was reasonably strong but not statistically significant ($0.05 < P < 0.10$, $o' = 3.75$). Neither the number of occurrences of ventricular tachycardia nor the number of ventricular premature depolarizations in the longest run placed patients at higher risk. The presence of supraventricular premature depolarizations, ventricular bigeminy, fusion beats, multiple configurations or pairs of ventricular premature depolarizations was not associated strongly with cardiac death in the 6 months after the acute myocardial infarction.

Bivariate Combinations

Combination of elevated creatine kinase and blood urea nitrogen: Table VI lists the 11 bivariate combinations most strongly associated with cardiac death within 6 months, as judged from the odds ratio. The combination of a peak creatine kinase level of 585 IU or greater and a blood urea nitrogen value of 20 mg/dl or greater most effectively divided the population into two strata with significantly different cardiac death rates for the first 6 months after acute myocardial infarction. The cardiac death rate of the 23 patients with both elevated creatine kinase and blood urea nitrogen levels was 48 percent compared with a rate of 5 percent for 77 patients with either or neither. The specificity rate of this stratification was 86 percent, the sensitivity rate 73 percent and the efficiency rate 84 percent.

Elevated blood urea nitrogen level and complex ventricular arrhythmia: There were several interesting results when variables obtained from the Holter recording were combined with a blood urea nitrogen level greater than 20 mg/dl. Of the 23 patients with at least 1 ventricular premature depolarization per hour and an elevated level of blood urea nitrogen, 9 (39 percent) died within the first 6 months compared with 6 of the 77 (8 percent) in the other group. Sixteen patients had R on T phenomenon and an elevated blood urea nitrogen level; this group had a death rate of 50 percent

TABLE VII

Prognostic Significance of Trivariates for Cardiac Death Within 6 Months After Acute Myocardial Infarction

Variables	2 × 2 Table (no. of patients)		Chi Square	Odds Ratio	Sensitivity (%)	Specificity (%)	Efficiency (%)
BUN-CK-LVF	11	9	27.57	20.58	73	89	87
	4	76					
BUN-CK-EH	9	7	21.72	15.30	60	92	87
	6	78					
BUN-EH-LVF	9	10	16.72	10.51	60	88	84
	6	75					
CK-EH-LVF	9	10	16.27	10.51	60	88	84
	6	75					
BUN-EH-VPD	8	8	15.18	10.33	53	91	85
	7	77					
BUN-LVF-VPD	7	9	9.81	7.10	47	89	83
	8	76					
EH-R on T-VPD	7	11	7.67	5.72	47	87	81
	8	74					

Abbreviations as in Table III.

within the first 6 months compared with 8 percent in the 84 patients who had either or neither of these two variables. Of 6 patients who had ventricular tachycardia and an elevated blood urea nitrogen level, 4 (67 percent) died within 6 months compared with 11 of 94 patients (12 percent) with either or neither variable. Although six is a very small number, the very high death rate (67 percent) and the σ' value (= 13.0) suggest that, were a larger group evaluated, this bivariate combination would be significantly related to cardiac death. These results indicate that patients with an elevated blood urea nitrogen level and complex ventricular arrhythmias are at very high risk of dying in the 6 months after acute myocardial infarction.

Trivariate Combinations

Trivariate combinations were analyzed with the two methods described. We present only the results of method I because it gave a more clearly defined relation with 6 month mortality than method II. Table VII lists the seven trivariate combinations most strongly associated with 6 month cardiac mortality as judged from the odds ratio. The best prognostic stratification was obtained using the values for peak creatine kinase and blood urea nitrogen at 2 weeks and the presence of left ventricular failure in the coronary care unit. At 6 months, 10 of the 19 patients (55 percent) with these characteristics had died. The 6 month cardiac death rate of the 71 patients who had none, one or two of these characteristics was only 5 percent. Of the 15 patients who died within 6 months of acute myocardial infarction, 10 had all three of these characteristics. This trivariate combination had a sensitivity rate of 73 percent, a specificity rate of 89 percent and an efficiency rate of 87 percent.

Discussion

In our study, the incidence of cardiac death in the 6 months after hospital discharge was almost four times greater than in the subsequent 6 months. Several other studies[1,4,18–20] also have indicated that the death rate for survivors of acute myocardial infarction is highest in the first 6 months after hospital discharge and declines substantially over the following 6 months. We therefore evaluated the predictive significance of variables for cardiac death within 6 months of acute myocardial infarction.

Comparison With Previous Studies

The cardiac death rate in our study of 15 percent for the first 6 months and 19 percent for the first year is comparable with the death rate found in several other studies. Norris et al.[6] found a 16 percent mortality rate in the first year after acute myocardial infarction; Vismara et al.[7] reported a sudden death rate of 14 percent for the first year. Schulze et al.[22] found a 10 percent rate of either ventricular fibrillation or sudden death during a mean follow-up period of 7.2 months. However, Van Durme and Pannier[10] reported a lower rate (8 percent) of sudden death within 1 year of acute myocardial infarction, and Moss et al.[23] found a 6 month mortality rate of only 6 percent, less than half of ours.

We did not find age a good predictor of early posthospital death after infarction. Moss et al.[3] found that age predicted cardiac death 1 1/2 to 2 years after acute myocardial infarction but not in the first 4 posthospital months.[4] Vismara et al.[7] also failed to find an association between age and cardiac death in the first posthospital year. As in previous studies,[5–7] the presence of "classic" coronary risk factors, such as hypertension, diabetes mellitus, obesity, hypercholesterolemia or smoking, was not a significant predictor of cardiac death within 6 months. Like several previous studies,[7,20,24] our study revealed no correlation between previous acute myocardial infarction or angina and sudden death in the posthospital phase of acute myocardial infarction.[7,20,24] However, other investigations[4,16,18] noted a significant correlation between history of angina and posthospital

mortality for periods of 2 months to 3 years. The differences among these studies may be caused partly by different criteria for diagnosis, duration and intensity of angina before acute myocardial infarction. It is also quite likely that the significance of a history of angina pectoris may be obscured by supply/demand changes in coronary blood flow that result from the index infarction.

We found that left ventricular failure in the coronary care unit and an enlarged heart on X-ray examination 2 weeks after acute myocardial infarction were predictors of early posthospital mortality. These characteristics reflect extensive myocardial damage or impaired myocardial function, or both. Norris et al.[6] and Beard et al.[18] noted that left ventricular failure was significantly more common in patients who died either early (1 to 2 months) or late (3 to 5 years) after their infarction. In the Health Insurance Plan (HIP) study,[1] left ventricular failure during acute myocardial infarction predicted early death (1 month) but not late death (4.5 years). Luria[25] and Vismara[7] and their coworkers concluded that left ventricular failure was not a significant risk factor. However, Luria et al. did find a higher rate of digitalis use among patients who later experienced cardiac death (10 percent in survivors and 40 percent in nonsurvivors).

Our finding that an elevated blood urea nitrogen level was a significant predictor of cardiac death is in agreement with the work of Luria et al.,[25] who found that this variable was the best predictor of death during follow-up of 143 patients after acute myocardial infarction. In contrast, Moss et al.[3] studied 100 patients after acute myocardial infarction and found no significant difference in the level of blood urea nitrogen between survivors and nonsurvivors. The disagreement among these studies may be partly due to differences in patient groups. Also, we found that an elevated uric acid level was significantly associated with cardiac death within 6 months. Ghosh et al.[26] found that, independent of use of diuretic agents, patients admitted for acute myocardial infarction had significantly higher uric acid concentrations than patients admitted for chest pain who did not have acute myocardial infarction. Both decreased renal urate excretion and elevated blood urea nitrogen concentrations after acute myocardial infarction could result from decreased renal perfusion due to reduced cardiac output. Although patients with increased blood urea nitrogen were twice as likely to have an elevated serum uric acid level, the association between these two variables was not statistically significant ($P > 0.05$, $o' = 2.1$).

Previous workers[27–30] *found an association between the peak creatine kinase level or infarct size index and in-hospital mortality from infarction.* We found a significant association between peak creatine kinase level in the coronary care unit and mortality in the first 6 posthospital months. We found increased predictive value by combining increased blood urea nitrogen 2 weeks after acute myocardial infarction and left ventricular failure in the coronary care unit with an elevated peak creatine kinase value. There was a 55 percent death rate in patients with all three of these characteristics, compared with a 5 percent mortality rate in other patients.

There have been conflicting reports[3,4,7,9,10,18,21,22,24] *about the possible relation between the occurrence of arrhythmias in the coronary care unit and cardiac death in the posthospital phase of acute myocardial infarction.* Like Vismara[7] and Luria[25] and their coworkers, we found that ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, occurring in the coronary care unit were not associated with increased risk of cardiac mortality within 6 months. The lack of association between ventricular arrhythmias in the coronary care unit and cardiac death within 6 months of acute myocardial infarction suggests that if a patient survives early electrical instability, his later course is not unfavorably altered.

Our results suggest that the occurrence of at least 1 ventricular premature depolarization per hour on a 24 hour continuous electrocardiographic recording 2 weeks after acute myocardial infarction increases the risk of cardiac death within 6 months, but the result was not statistically significant. Similarly, Luria et al.[25] found a significantly higher death rate during a 2 year follow-up in patients with 1 or more ventricular premature depolarizations in an 8 hour recording made 2 weeks after acute myocardial infarction. Moss et al.[4] found a significantly higher cardiac death rate in patients with 20 or more ventricular premature depolarizations per hour (6 hour recording 2 weeks after infarction). However, only 8 percent of their patients had 20 or more ventricular premature depolarizations per hour, and only 3 of the 11 cardiac deaths occurred in this group. Vismara et al.[7] found that complex ventricular arrhythmias (defined as more than 5 ventricular premature depolarizations per minute, multiformed ventricular premature depolarizations, R on T phenomenon or two or more consecutive ventricular premature depolarizations) in 10 hour Holter recordings predicted an increased cardiac death rate, whereas simple ventricular arrhythmias did not. Van Durme and Pannier[10] evaluated patients with an 8 hour electrocardiographic recording 1 month after infarction and followed them up for 1 year. They found that 75 percent of those who died suddenly had 60 or more ventricular premature depolarizations per hour. Schulze et al.[21,22] obtained a 24 hour Holter recording and a radionuclide ejection fraction in 88 patients just before discharge after acute myocardial infarction. All eight sudden deaths that occurred in 7 months of follow-up were in patients with both a left ventricular ejection fraction of less than 40 percent and complex ventricular premature depolarizations. There is reasonably good agreement among these studies that frequent or complex ventricular premature depolarizations recorded in the late hospital phase of acute myocardial infarction are predictors of early posthospital cardiac death, particularly if accompanied by significant left ventricular dysfunction.

Moss et al.[4] *previously used multivariate prognostic stratification to identify a high risk group.* They found

a 19 percent cardiac mortality rate within 4 months of acute myocardial infarction among patients who had two or three of the following characteristics: 20 or more ventricular premature depolarizations per hour, history of angina on moderate activity or at rest, and hypotension or heart failure, or both, in the coronary care unit. Patients with none or one of the three variables had a 2 percent mortality rate. Although we used similar methods to analyze our data, our results differ greatly from theirs; their best multivariate set of predictors was not significantly associated with 6 month cardiac mortality in our patients. This difference could be attributable to the very significant differences between their patients and ours. Their patients were younger (they enrolled no patients older than 65, we had 39 patients over this age), healthier (4 percent 4 month cardiac mortality rate compared with our 10 percent) and mostly white (97 percent compared with our 58 percent). Moreover, their study was conducted in suburban community hospitals, and ours was done in an urban university hospital. Nevertheless, the lack of cross-validation is distressing in that it raises questions about the general applicability of stratification results obtained in a single medical center.

Implications

In this study we achieved considerable success in finding combinations of variables that identify acute myocardial infarction patients at very high or very low risk for cardiac death in the early posthospital period. Risk stratification has several purposes. We want to identify postinfarction patients who are at very low risk in order to avoid exposing this group to the hazards of even low risk interventions such as drug therapy. Conversely, a group at very high risk may be suitable for an intervention with significant morbidity or mortality, or both, such as cardiac surgical intervention. Also, it may be desirable to select a high risk group that lacks a certain risk factor because that factor precludes the intervention being contemplated; for example, high risk patients who lack severe left ventricular dysfunction could be enrolled in beta receptor blocker intervention trials. For the future, risk stratification using functionally recognizable categories, such as arrhythmia, ischemia and ventricular dysfunction, should be more fully explored. High risk groups identified in this way readily suggest strategies for clinical treatment or intervention trials. Also, further clarification of the mechanisms by which risk factors affect mortality will be extremely useful in planning the means to prevent mortality in the year after acute myocardial infarction. Improved risk stratification and better understanding of risk mechanisms should also significantly reduce the cost of preventing cardiac death during the early posthospital period of acute myocardial infarction by permitting better selection of interventions and treatment groups.

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References

1. **Weinblatt E, Shapiro S, Frank CW, et al:** Prognosis of men after first myocardial infarction: mortality and first recurrence in relation to selected parameters. Am J Public Health 58:1329–1335, 1968
2. **Pell S, D' Alonzo CA:** Immediate mortality and five year survival of employed men with a first myocardial infarction. N Engl J Med 270:915–922, 1964
3. **Moss AJ, DeCamilla J, Engstrom F, et al:** The post-hospital phase of myocardial infarction: identification of patients with increased mortality risk. Circulation 49:460–466, 1974
4. **Moss AJ, DeCamilla J, Davis H, et al:** The early posthospital phase of myocardial infarction: prognostic stratification. Circulation 54:58–64, 1976
5. **Peel AAF, Semple T, Wang I, et al:** A coronary prognostic index for grading the severity of infarction. Br Heart J 24:745–760, 1962
6. **Norris RM, Caughey DE, Mercer CJ, et al:** Coronary prognostic index for predicting survival after recovery from acute myocardial infarction. Lancet 2:485–488, 1970
7. **Vismara LA, Amsterdam EA, Mason DT:** Relation of ventricular arrhythmias in the late hospital phase of acute myocardial infarction to sudden death after hospital discharge. Am J Med 59:6–12, 1975
8. **Leren P, Hjermann I, Bjornson J:** Prognostic significance of electrocardiographic changes in survivors of myocardial infarction. Acta Med Scand 188:523–526, 1970
9. **Coronary Drug Project Research Group:** Prognostic importance of premature beats following myocardial infarction. JAMA 223: 1116–1124, 1973
10. **Van Durme J-P, Pannier RH:** Prognostic significance of ventricular dysrhythmias 1 year after myocardial infarction (abstr). Am J Cardiol 37:178, 1976
11. **Nelson G, Cohn P, Gorlin R:** Prognosis in medically treated coronary artery disease: the value of ejection fraction compared with other measurements (abstr). Clin Res 22:685, 1974
12. **Nie N, Bent DH, Hull CA:** Statistical Package for Social Sciences. New York, McGraw-Hill, 1970
13. **Feinstein AR:** Clinical biostatistics. XV. The process of prognostic stratification (Part I). Clin Pharmacol Ther 13:442–457, 1972
14. **Feinstein AR:** Clinical biostatistics. XVI. The process of prognostic stratification (Part II). Clin Pharmacol Ther 13:609–624, 1972
15. **Feinstein AR:** Clinical biostatistics. XVII. Synchronous partition and bivariate evaluation in predictive stratification. Clin Pharmacol Ther 13:755–768, 1972
16. **Fleiss JL:** Statistical Methods for Rates and Proportions. New York, John Wiley, 1973
17. **Galen RS, Gambino SR:** Beyond Normality: the Predictive Value and Efficiency of Medical Diagnosis. New York, John Wiley, 1975
18. **Beard OW, Hipp HR, Robins M, et al:** Initial myocardial infarction among 503 veterans. Am J Med 28:871–883, 1960
19. **Vedin JA, Wilhelmsson C, Elmfeldt D, et al:** Sudden death: identification of high risk groups. Am Heart J 86:124–132, 1973
20. **Gazes PC, Kitchell JR, Meltzer LE, et al:** Death rate among 795 patients in the first year after myocardial infarction. JAMA 197: 906–908, 1966
21. **Schulze RA, Rouleau J, Rigo P, et al:** Ventricular arrhythmias in the late hospital phase of acute myocardial infarction. Circulation 52:1006–1011, 1975
22. **Schulze RA Jr, Strauss HW, Pitt B:** Sudden death in the year fol-

Clinicopathologic Analysis of Cardiac Dysfunction in 52 Patients With Sickle Cell Anemia

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Clinical studies have long suggested the presence of a specific cardiomyopathy in sickle cell anemia secondary to intracoronary thrombosis and subsequent infarction. Fifty-two autopsy patients were studied (48 with SS hemoglobin, 4 with S-C or S-Thal hemoglobin) to ascertain the range of cardiac pathologic abnormalities associated with this disease. The average age was 17 years (range 1 month to 48 years). Renal failure and infection were the most common causes of death; the former was a more common cause in adults than in children. Right and left ventricular hypertrophy and dilatation were the most common abnormal pathologic findings. No evidence of recent or remote myocardial infarction, coronary thrombosis or arteritis was noted in any patient. Eight patients who were studied with postmortem coronary arteriograms exhibited markedly increased coronary arterial caliber with no evidence of atherosclerosis.

Seventeen of the 52 patients studied had clinical evidence of congestive heart failure before death. Of these 17 patients, 7 had moderate to severe left ventricular hypertrophy associated with chronic renal failure and hypertension, 2 had right ventricular hypertrophy with organized pulmonary thrombosis, 2 had rheumatic mitral valve disease and 2 died during the second trimester of pregnancy. Two of the 17 patients thought to have pulmonary edema before death in fact had aspiration pneumonia and hemorrhagic pneumonitis, respectively. The data suggest that cardiac dysfunction in sickle cell anemia can usually be explained by the adverse effect of coexisting disease on the diminished cardiac reserve of chronic anemia. The data do not support the concept of a specific "sickle cell cardiomyopathy."

The diagnosis of congestive heart failure is often difficult in patients with sickle cell anemia. Dyspnea and fatigue, together with cardiac murmurs, gallop rhythms and cardiomegaly, are common in these patients and often so striking as to suggest left ventricular dysfunction.[1–4] Thrombosis of small intracardiac blood vessels by aggregates of sickled erythrocytes is cited as a possible mechanism for the production of left ventricular dysfunction in these patients.[5] However, the evidence supporting thrombosis and subsequent myocardial infarction is scant.[6,7] This study analyzes the cardiac findings in 52 patients with sickle hemoglobin examined at autopsy. The findings in the patients with clinical evidence of congestive heart failure are compared with those in patients without evidence of failure. The data suggest that patients with congestive heart failure usually have severe coexisting disease secondarily affecting myocardial function rather than a cardiomyopathy specific for sickle cell anemia.

Methods

Patients: The data were reviewed on all patients with the diagnosis of sickle cell anemia subjected to autopsy from 1915 to 1977 at The Johns Hopkins Hospital. Patients who died before the introduction of hemoglobin electro-

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phoresis were included if the clinical history described chronic hemolytic anemia and jaundice with sickled erythrocytes on blood smears. Patients with mild anemia, hemolysis and sickled erythrocytes noted on blood smears who had attacks of bone or abdominal pain, or both, but whose spleen was noted to be normal or enlarged at autopsy were considered to have either SC or S-Thal disease. The records of each autopsy patient were reviewed for clinical signs of cardiac dysfunction, including a history of congestive heart failure, pulmonary edema or arrhythmia. Retrospective analysis of the data on congestive heart failure was not attempted. Patients were considered to have congestive heart failure if this diagnosis had been specifically considered by physicians in attendance before death. Generally this diagnosis was based on the presence of dyspnea, orthopnea, pedal edema, rales and gallop rhythms. Patients presenting with pain in the limbs, back, chest or abdomen in association with normal or slightly elevated temperature and the passage of dark urine were considered to have died in crisis if no other cause of death was evident at autopsy. Patients 16 years of age or older at the time of death were classified into Group I (adults); younger patients were classified into Group II (children).

Pathologic examination: The clinical and autopsy records and histologic slides including sections of heart, lung, liver, spleen, kidney and bone for each patient were reviewed, and a primary cause of death was decided on for each patient. Gross specimens available from 13 patients were also reviewed. In the adult group a heart weighing less than 350 g was considered normal, one weighing 350 to 500 g moderately enlarged and one weighing more than 500 g markedly enlarged. Left ventricular hypertrophy was noted when the heart was enlarged as assessed from heart weight and the left ventricular free wall thickness was greater than 1.5 cm. Ventricular dilatation was considered present when specifically mentioned in the gross description and when observed in the gross specimen and photographs. In eight patients, the heart had been studied after postmortem arteriography and formalin fixation in a distended state.[8] The diameter of a theoretical single coronary artery (D_{Th}) supplying the heart was determined by measuring the diameters of the right (D_R) and left (D_L) coronary arteries from the arteriograms and applying the formula:

$$(D_{Th})^3 = (D_R)^3 + (D_L)^3$$

The derivation and use of this measure of coronary caliber is described elsewhere.[9]

Results

Clinical features: The average age of the 52 patients studied was 17 years, and 24 of the patients (46 percent) were male (Table I). Hemoglobin electrophoresis, performed in 31 of the 52 patients, confirmed the presence of SS hemoglobin in 30 and SC hemoglobin in 1. Eighteen of the remaining 21 patients studied had a clinical course compatible with sickle cell disease (SS hemoglobin), and 3 had in addition splenomegaly suggesting S-C or S-Thal hemoglobin. The children's group consisted of 14 boys and 13 girls whose average age was 5.4 years (range 5 months to 15 years). Congestive heart failure and renal disease were much more common in the adult than in the children's group (Table I).

Systolic murmurs were heard in 58 percent of the patients who did not die suddenly at home or immediately on entry into the hospital. A systolic murmur was present in 76 percent of the patients with congestive heart failure. A diastolic murmur was described in three patients, only one of whom had rheumatic heart disease. All three patients with a diastolic murmur had congestive heart failure before death.

Renal failure and infection were the most common causes of death (Table II). Infection was the most common cause of death in the children's group; death from renal failure was more common in adults. Of the six patients who died from renal failure, two had papillary necrosis at autopsy, two had lesions compatible with chronic glomerulonephritis, one had extreme arteriosclerosis with parenchymal fibrosis and one had widespread scarring of uncertain origin. Other causes of death included congestive heart failure in two patients (Patients 1 and 6, Table III), hemorrhage related to pregnancy or surgery in three and infectious complications after surgery in three.

Postmortem cardiac findings: Table IV lists the cardiac findings at autopsy in the two groups. Right and left ventricular dilatation was common in both adults and children; however, right and left ventricular hypertrophy was more common and more severe in adults. Of the nine adults with left ventricular hypertrophy, five had severe hypertrophy, and four of these five had a history of hypertension in the presence of chronic renal failure.

TABLE I
Clinical Features of 52 Patients With Sickle Cell Anemia

	Group I (adults) (25 patients)	Group II (children) (27 patients)
Mean age and range (yr)	29 (16–48)	5.4 (0.4–15)
Male/female ratio	10/15	14/13
Hematocrit (mean and range of values before death) (%)	19 (12–46)	20 (5–32)
Congestive heart failure before death (no. of patients and % of group)	14 (56%)	3 (11%)
Hypertension (history of blood pressure >90 mm Hg diastolic) (no. of patients and % of group)	6 (24%)	3 (11%)
Renal disease (history of blood urea nitrogen >50 mg/dl) (no. of patients and % of group)	8 (25%)	1 (4%)

TABLE II
Causes of Death

	Group I (adults) (25 patients)	Group II (children) (27 patients)
Congestive heart failure	2	0
Renal failure	5	1
Infection	6	11
Cerebral lesion	1	1
Respiratory failure	3	1
Crisis	4	8
Hemorrhage	3	0
Miscellaneous	1	5
Total	25	27

TABLE III
Clinical and Pathologic Findings in 17 Patients With Sickle Cell Anemia and Clinical Diagnosis of Congestive Heart Failure

Case no.	Age (yr) & Sex	HCT	Clinical Features	Pathologic Findings
1	29F	25	Pregnant (second trimester)	Active myocarditis, cardiac hemosiderosis, moderate LVH
2	19M	15	Hypertension, chronic renal failure	Fibrinous pericarditis, severe LVH
3	28F	13	Chronic renal failure	Moderate LVH
4	33M	20	Hypertension, chronic renal failure	Severe LVH, rheumatic MV disease
5	42F	16	Hypertension, chronic renal failure	Severe LVH
6	30M	19	History of dyspnea, crisis	RVH, organized pulmonary thrombi
7	32F	29	Staphylococcal sepsis, pulmonary edema	Fibrinous pericarditis, rheumatic MV disease
8	29F	46	Dyspnea	RVH, organized pulmonary thrombi
9	23F	10	Pregnant (second trimester), tuberculosis	Moderate LVH
10	46F	15	Postoperative abscess, uremia, hypertension	Fibrinous pericarditis, moderate LVH
11	48M	16	Multiple myeloma	Hemorrhagic pneumonia, moderate LVH
12	19M	19	Recurrent pulmonary emboli	Severe RVH, pulmonary fibrosis
13	18M	15	Crisis	Aspiration pneumonitis
14	21M	12	Hypertension, chronic renal failure	Severe LVH
15	9F	20	Crisis, history of hypertension	RVH and dilatation, LVH
16	4F	5	Aplastic crisis, transfusion before death	Mild left and right ventricular dilatation
17	15M	11	Hypertension, chronic renal failure	Moderate LVH, fibrinous pericarditis

HCT = hematocrit; LVH = left ventricular hypertrophy; MV = mitral valve; RVH = right ventricular hypertrophy.

TABLE IV
Cardiac Pathologic Findings in Sickle Cell Anemia

	Adults (25 patients)		Children (27 patients)	
	no.	%	no.	%
Left ventricular				
Dilatation	11	44	8	30
Hypertrophy	9	36	6	22
Right ventricular				
Dilatation	16	64	13	48
Hypertrophy	9	36	6	22
Pericarditis	3	12	1	4
Myocarditis	1	4	3	11
Rheumatic valve disease	1	4	1	4
Myocardial scarring (focal)	3	12	1	4
No cardiac disease	3	12	7	26

Myocarditis was present in one adult patient (Fig. 1). The condition occurred in the second trimester of pregnancy and was associated with marked cardiac hemosiderosis. Three children also had myocarditis: one died suddenly of unknown cause, one of meningococcemia and the third of myocarditis that appeared to be syphilitic in origin. *Pericarditis*, noted in four patients, occurred in association with renal failure in three and with sepsis in one.

Valvular heart disease was present in two adult patients, and in both patients the thickened mitral leaflets with commissural fusion and thickened chordae tendineae were compatible with rheumatic heart disease. Microscopic myocardial scarring, focal in nature, was present in two adults and one child. No patient had evidence of recent or remote myocardial infarction, coronary arteritis, emboli, thrombosis or atherosclerosis.

Clinical congestive failure: postmortem findings: Seventeen of the 52 patients studied had clinical evidence of congestive heart failure (Table III). Seven of these 17 patients had chronic renal failure, which was associated with fibrinous pericarditis in 3 patients, hypertension in 6 and moderate to severe left ventricular hypertrophy in 4. Two of the 17 patients were in the second trimester of pregnancy. One patient had severe cardiac hemosiderosis and myocarditis (Fig. 1). Cor pulmonale was present in three patients (Fig. 2). Pathologic evidence of rheumatic mitral valve disease was noted in two patients. Two patients were thought clinically to have pulmonary edema but at autopsy were noted to have an aspiration pneumonitis and hemorrhagic pneumonia, respectively. Mild left and right ventricular dilatation only was noted at autopsy in two patients, one of whom had received a blood transfusion before congestive heart failure developed.

Of the 35 patients who did not have clinical evidence of congestive heart failure, 19 at autopsy had mild to moderate right and left ventricular dilatation and hypertrophy, 1 had severe left ventricular hypertrophy

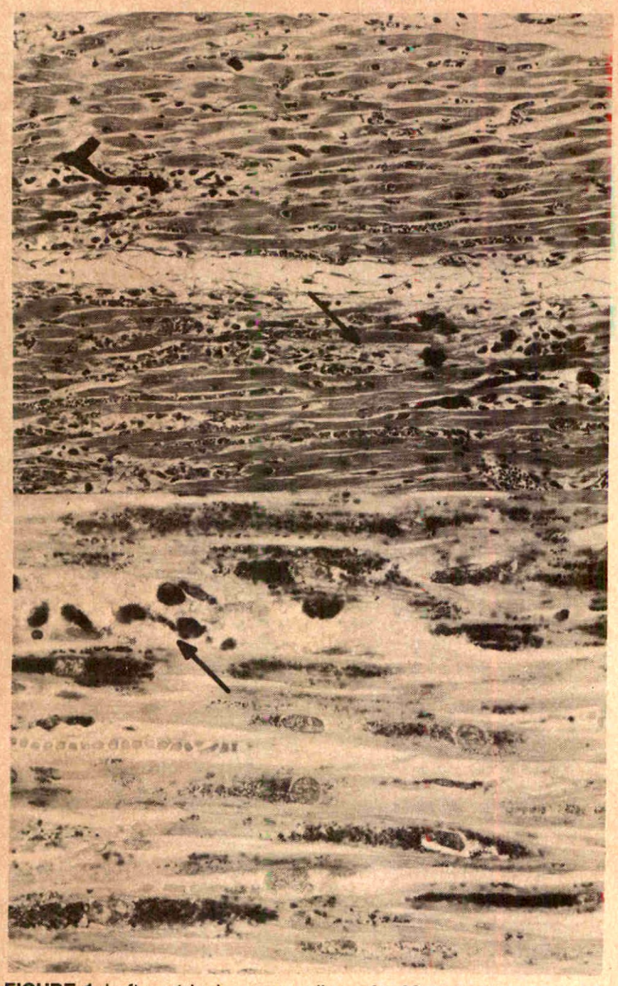

FIGURE 1. Left ventricular myocardium of a 29 year old patient with SS hemoglobin who had been maintained on a chronic transfusion program and was 4 months pregnant at the time of death. **Top,** there is a focal myocarditis (**arrow**) with loss of individual muscle cells and groups of cells and an acute inflammatory cell infiltration. The dark material is injection mass within dilated arterioles and capillaries (hematoxylin-eosin ×150, reduced by 27 percent). **Bottom,** the cardiac muscle cells contain abundant hemosiderin, particularly in perinuclear positions. Macrophages in the areas of muscle cell loss also contain large quantities of iron (**arrow**). It is unknown whether the muscle cell necrosis is caused by the iron accumulation or, more probably, by a coexistent injury, possibly a viral myocarditis (iron stain ×500, reduced by 27 percent).

and 11 had a normal-appearing heart. Myocarditis, present in two patients, was focal in one and diffuse in the second, occurring in the latter with severe bacterial pneumonia. Rheumatic mitral valve disease was present in one patient. A punctate myocardial hemorrhage was noted in one patient who had numerous systemic fat emboli.

Postmortem coronary arteriography: In the eight cases in which a postmortem coronary arteriogram (Fig. 3) was available for study, heart weight ranged from 320 to 900 g (average 517). The diameter calculated for the

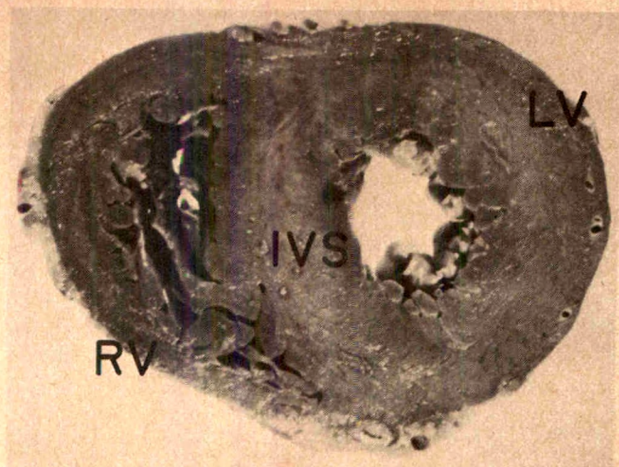

FIGURE 2. Transverse section of the right (RV) and left (LV) ventricles of a 40 year old man with SC hemoglobin. The heart, which weighed 450 g, shows right ventricular hypertrophy. IVS = interventricular septum.

theoretical single coronary artery (D_{Th}) ranged from 4.9 to 8.0 mm (average 6.7 ± 1.1 mm [standard deviation]). In a previous study[9] we showed in a group of 145 hearts with normal coronary arteries that the D_{Th}, determined as for the hearts studied here, was 5.8 ± 1.0 mm (range 3.0 to 8.6). The heart weight, which is closely correlated with coronary caliber, ranged from 110 to 1,230 (average 538) for the 145 hearts. Because the heart weights in the two groups are similar, comparison of coronary calibers shows that the D_{Th} for patients with sickle cell disease is significantly larger ($P < 0.01$ by Student's t test).

Discussion

Proposed mechanisms for myocardial dysfunction in sickle cell anemia: The cardiovascular abnormalities of sickle cell anemia have been widely discussed since the disease was first described in 1910 by Herrick.[10] The often striking systolic murmurs and gallop rhythms, together with an enlarged cardiac silhouette and electrocardiographic repolarization abnormalities, combine to suggest left ventricular dysfunction in many of these patients.[4] Although the hyperkinetic circulation found with chronic anemia of any cause may produce many of these findings,[11] congestive heart failure is cited as a complication of sickle cell anemia.[5] Although cor pulmonale secondary to recurrent pulmonary thrombosis is established as a complication of this disease,[12,13] it has been suggested that myocardial dysfunction caused by thromboses of small intracardiac vessels with subsequent infarction can occur.[5] In addition, an ill defined coronary arteritis has been described in limited pathologic reports and has been proposed as a cause of myocardial disease.[5] However, the evidence supporting these proposed mechanisms for myocardial dysfunction rests on isolated case reports and limited pathologic studies.[6,7]

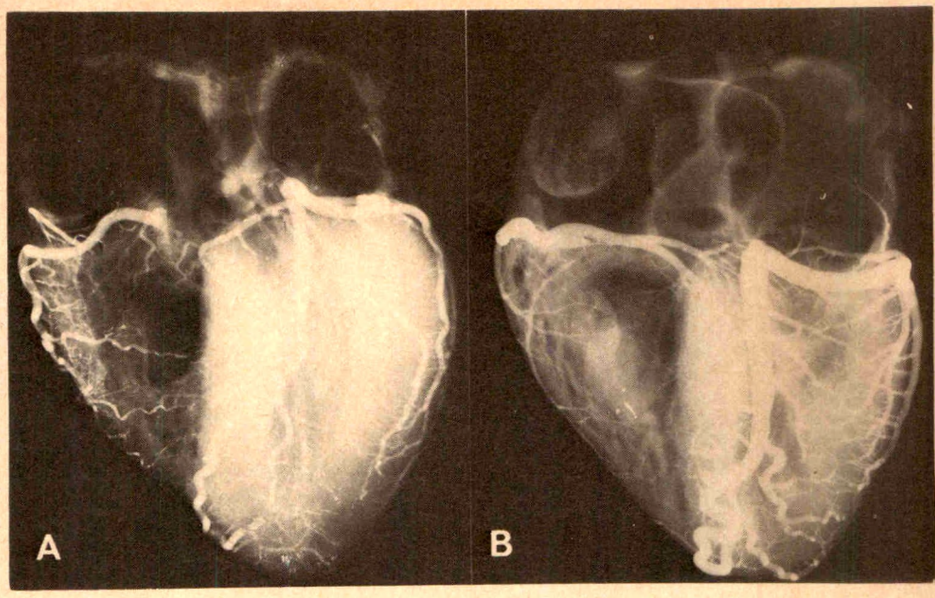

FIGURE 3. Coronary arteriograms. **A,** postmortem radiograph of the 420 g heart of a 42 year old woman with SS hemoglobin. The coronary caliber is within the normal range for similar-sized hearts of patients without sickle cell disease. **B,** radiograph of the 350 g heart of a 16 year old youth with SS hemoglobin. The coronary arteries have marked increase of caliber. Despite the dilatation there is no increase in epicardial coronary arterial tortuosity.

Left ventricular function is difficult to evaluate clinically in sickle cell anemia because weakness, fatigue and dyspnea together with gallop rhythms are commonly present and probably represent systemic effects of chronic anemia rather than true congestive heart failure in many patients. In a recent study of patients with sickle cell anemia, ejection phase indexes of left ventricular function were measured using echocardiography,[14] and no differences were observed in ejection fraction or velocity of circumferential fiber shortening between patients with sickle cell anemia and normal control patients. Furthermore, with these same indexes no differences were detectable between older and younger patients with sickle cell anemia.[14]

Although previously described autopsy findings have included right and left ventricular dilatation, increased heart weight,[1,4] ill defined arteritis in the presence of intracoronary aggregates of sickled erythrocytes[6,7] and a peculiar cardiomyopathy,[15,16] most reports have been based on a small number of patients. In our consecutive nonselected series, cardiac abnormalities were frequent; however, when present they appeared to be secondary to associated disease or an unrelated illness.

Role and mechanisms of congestive heart failure: In our study clinical evidence of congestive heart failure was present in 17 patients (33 percent) and was noted more often in adults than in children. This is consistent with the findings of a recent demographic study showing that infection is a more frequent cause of death in children, whereas complicated illnesses with multiorgan failure are a more frequent cause of death in adults.[17] There were striking differences in the cardiac pathologic findings in the groups dying with and without congestive heart failure. Of the 17 patients who had a clinical history of congestive heart failure, 8 (47 percent) had heart failure in the setting of hypertension or chronic renal failure, 3 had cor pulmonale and 2 had rheumatic heart disease. In 14 of these 17 patients with heart failure, marked ventricular hypertrophy with or without dilatation was present at autopsy, but in each case the hypertrophy was associated with noncardiac sickle cell disease or with coexisting non-sickle cell disease. Two of the three patients with less severe cardiac abnormalities had lung disease that probably easily masqueraded as pulmonary edema when viewed in conjunction with the cardiomegaly and gallop rhythm of the associated chronic anemia. These two cases underscore the difficulty of diagnosing congestive heart failure in sickle cell anemia in the presence of severe coexisting disease. In no heart was myocardial infarction or myocardial fibrosis noted.

Coronary arterial findings: The examined coronary arteries were normal, with no evidence of arteritis, in situ thrombosis, embolism or atherosclerosis. Furthermore, the small intramural coronary arteries were normal. Of interest were the "supernormal" coronary arteries in the patients who had postmortem angiograms. The coronary tree in these patients was not only widely patent, but of increased caliber compared with that in a series of hearts of comparable weight and normal coronary arteries. The significance of such supernormal coronary arteries in this disease is not known, but it may be a response to chronic anemia and increased blood volume. Whether the absence of atherosclerosis in these patients is significant is not known because the average age of the adults was only 29 years. Nevertheless, the five patients over age 40 years had no evidence of coronary atherosclerosis.

Implications: These data suggest that hypertensive cardiovascular disease in association with renal failure, cor pulmonale secondary to pulmonary hypertension and changes in blood volume associated with pregnancy

and transfusion therapy suffice to explain most episodes of congestive heart failure. The findings do not support the existence of a specific "sickle cell cardiomyopathy." They do suggest that patients with sickle cell anemia are at risk of having congestive heart failure associated with the diminished cardiac reserve of chronic anemia but precipitated by coexisting disease. We conclude that patients with sickle cell anemia and congestive heart failure should be investigated fully for the precipitating causes of the failure before they are labeled as having "sickle cell cardiomyopathy."

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References

1. **Klinefelter HF:** The heart in sickle cell anemia. Am J Med Sci 203:34–51, 1942
2. **Henderson AB:** Sickle cell anemia. Clinical study of 54 cases. Am J Med 9:757–765, 1950
3. **Margolies MP:** Sickle cell anemia. A composite study and survey. Medicine (Baltimore) 30:357–443, 1951
4. **Uzsoy NK:** Cardiovascular findings in patients with sickle cell anemia. Am J Cardiol 13:320–328, 1964
5. **Hurst JW:** The Heart. New York, McGraw-Hill, 1974, p 1362
6. **Oliveira E, Gomez-Patino N:** Falcemic cardiomyopathy. Report of a case. Am J Cardiol 11:686–688, 1963
7. **Winsor T, Burch GE:** The electrocardiogram and cardiac state in active sickle-cell anemia. Am Heart J 29:685–696, 1945
8. **Hutchins GM, Anaya OA:** Measurements of cardiac size, chamber volumes, and valve orifices at autopsy. Johns Hopkins Med J 133:96–106, 1973
9. **Hutchins GM, Bulkley BH, Miner MM, et al:** Correlation of age and heart weight with tortuosity and caliber of normal human coronary arteries. Am Heart J 94:196–202, 1977
10. **Herrick JB:** Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia. Arch Intern Med 6:517–521, 1910
11. **Varat MA, Adolph RJ, Fowler NO:** Cardiovascular effects of anemia. Am Heart J 83:415–426, 1972
12. **Yater WM, Hansmann GH:** Sickle-cell anemia: a new cause of cor pulmonale. Report of two cases with numerous disseminated occlusions of the small pulmonary arteries. Am J Med Sci 191: 474–484, 1936
13. **Moser KM, Shea JG:** The relationship between pulmonary infarction, cor pulmonale and the sickle states. Am J Med 22: 561–579, 1957
14. **Gerry JL, Baird MG, Fortuin NJ:** Evaluation of left ventricular function in patients with sickle cell anemia. Am J Med 60:968–972, 1976
15. **Rubler S, Fleischer RA:** Sickle cell states and cardiomyopathy. Sudden death due to pulmonary thrombosis and infarction. Am J Cardiol 19: 867–873, 1967
16. **Fleischer RA, Rubler S:** Primary cardiomyopathy in nonanemic patients. Association with sickle cell trait. Am J Cardiol 22: 532–537, 1968
17. **Powers DR:** Natural history of sickle cell disease. The first ten years. Semin Hematol 12:267–285, 1975

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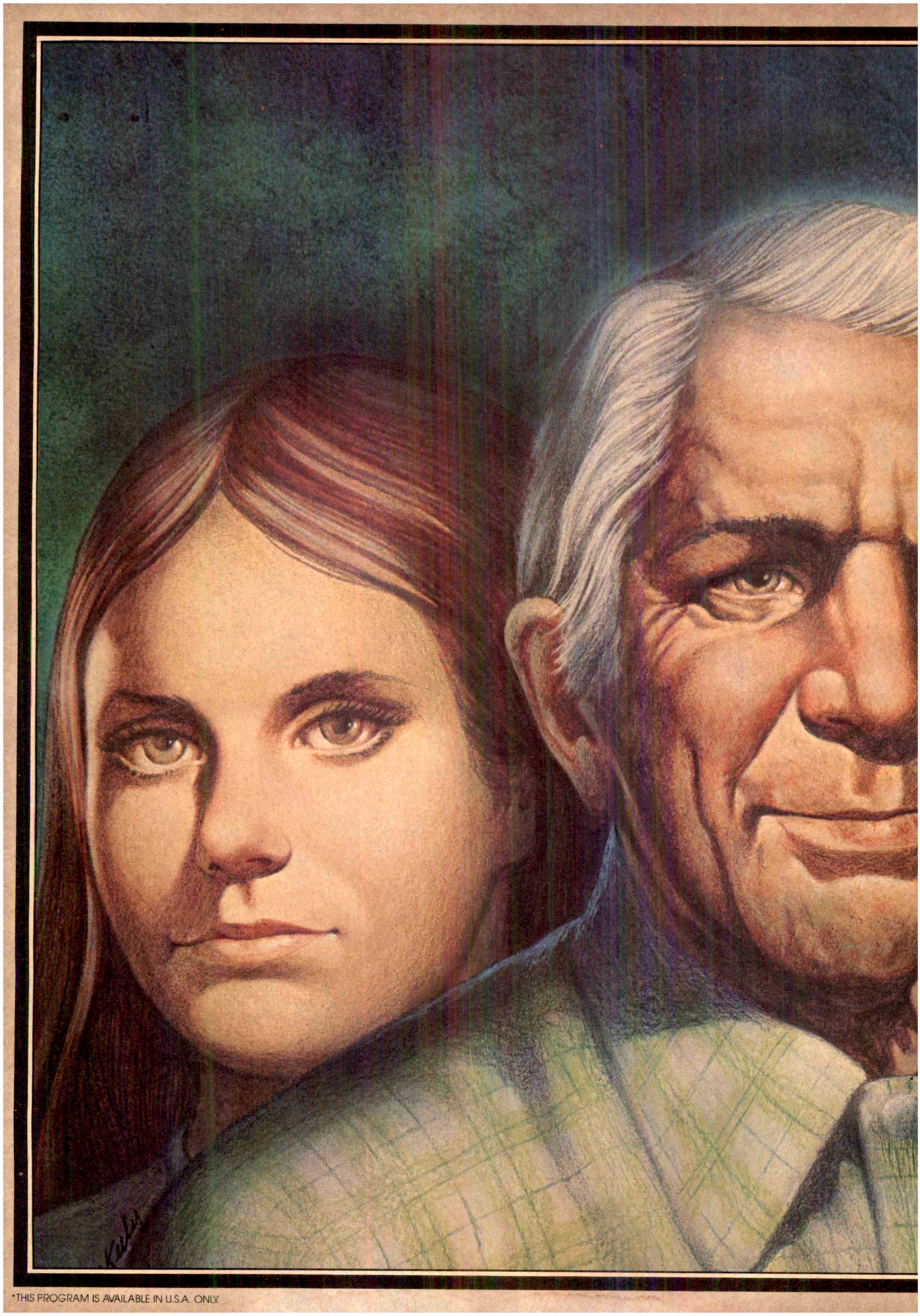

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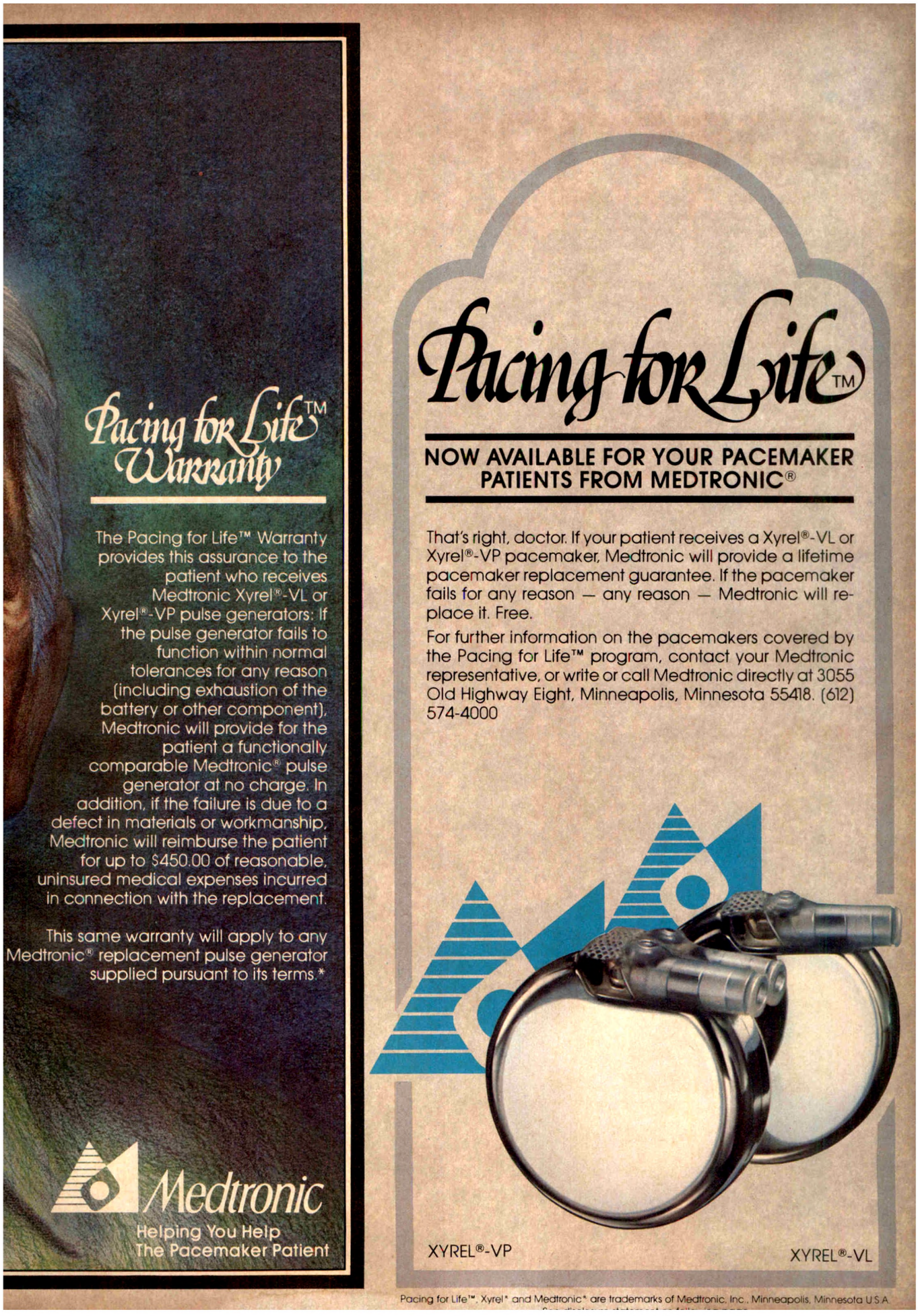
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Helping You Help The Pacemaker Patient
Pacing for Life™
NOW AVAILABLE FOR YOUR PACEMAKER PATIENTS FROM MEDTRONIC®
That's right, doctor. If your patient receives a Xyrel®-VL or Xyrel®-VP pacemaker, Medtronic will provide a lifetime pacemaker replacement guarantee. If the pacemaker fails for any reason — any reason — Medtronic will replace it. Free.
For further information on the pacemakers covered by the Pacing for Life™ program, contact your Medtronic representative, or write or call Medtronic directly at 3055 Old Highway Eight, Minneapolis, Minnesota 55418. (612) 574-4000
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XYREL®-VL
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MEDTRONIC®
IMPLANTABLE PULSE GENERATORS

INTENDED USES

Ventricular pacing using an implantable ventricular pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation or conduction disorders leading to bradyarrhythmias, tachyarrhythmias and heart block (see product labeling for detailed list of intended uses).

CONTRAINDICATIONS

There are no known contraindications to the use of pacing as a therapeutic modality for the control of heart rate. The patient's age and medical condition, however, may dictate the particular pacing systems and implantation procedure used by the physician.

WARNINGS

Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of unipolar pulse generators or bipolar pulse generators implanted in the unipolar mode because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator.

PRECAUTIONS

The physician should be aware that all pulse generators will ultimately cease to function, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, and elevated thresholds, and that proper operation may be affected by electrical interference from equipment using electrical energy, or medical complications.

SIDE EFFECTS

Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.

Medtronic

Medtronic, Inc.
3055 Old Highway Eight
Minneapolis, MN 55418

Prescribe Tunturi exercise for your patient Work is measured in a watt load range of 25 300w at 50 rpm. The Tunturi is quiet, affordab and portable, with quality Finnish constru tion. It's rehabilitation your patients can li with.

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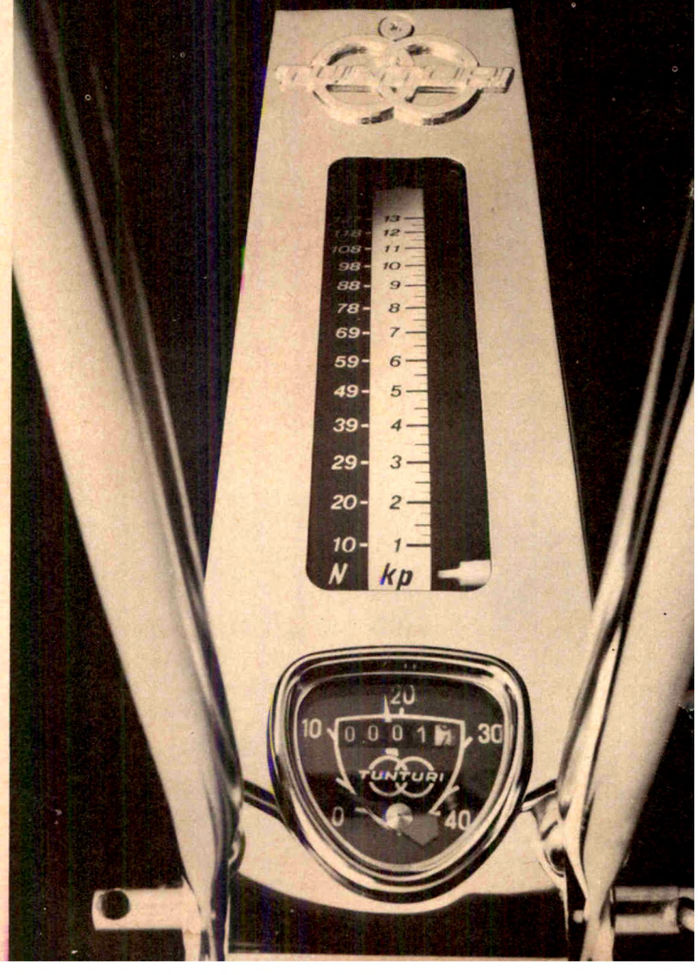
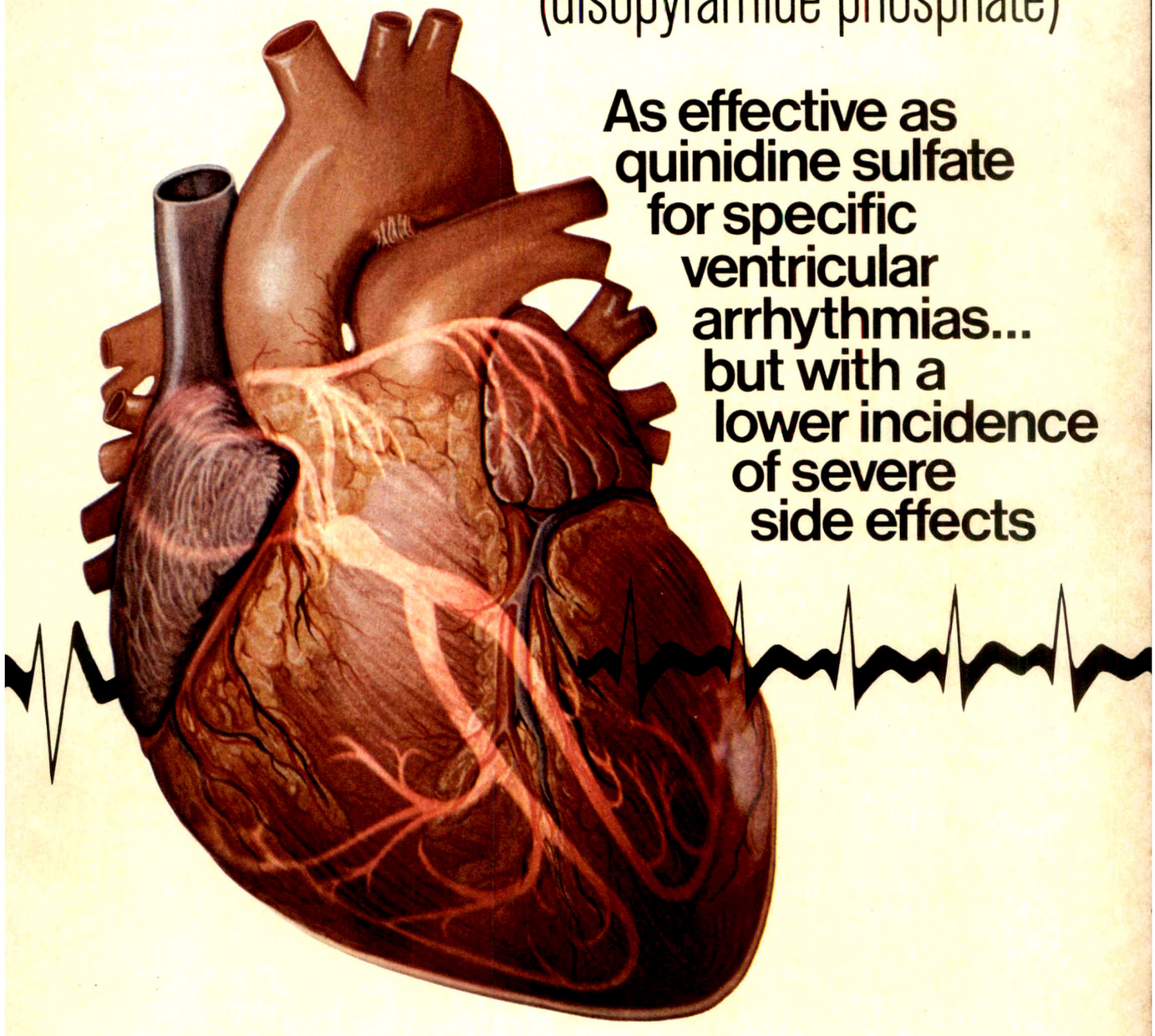
Controlled Exercise



From Searle

Norpace®

(disopyramide phosphate)



As effective as quinidine sulfate for specific ventricular arrhythmias... but with a lower incidence of severe side effects

Efficacy thoroughly proved and documented—no other antiarrhythmic agent subjected to such rigidly controlled study prior to introduction

Effective in specific ventricular arrhythmias—indicated in premature ventricular contractions (PVCs): unifocal, multifocal or paired PVCs or episodes of ventricular tachycardia (VT)

Excellent patient tolerance—lower incidence of severe side effects than quinidine . . . and significantly better tolerated

Dose-related plasma levels—plasma levels correlate closely with dosage

Norpace effect on hemodynamics—rarely alters blood pressure significantly at recommended oral doses, and may reduce cardiac output by about 10%

Please see next page for a brief summary of prescribing information.

In specific ventricular arrhythmias...proved

Norpace®

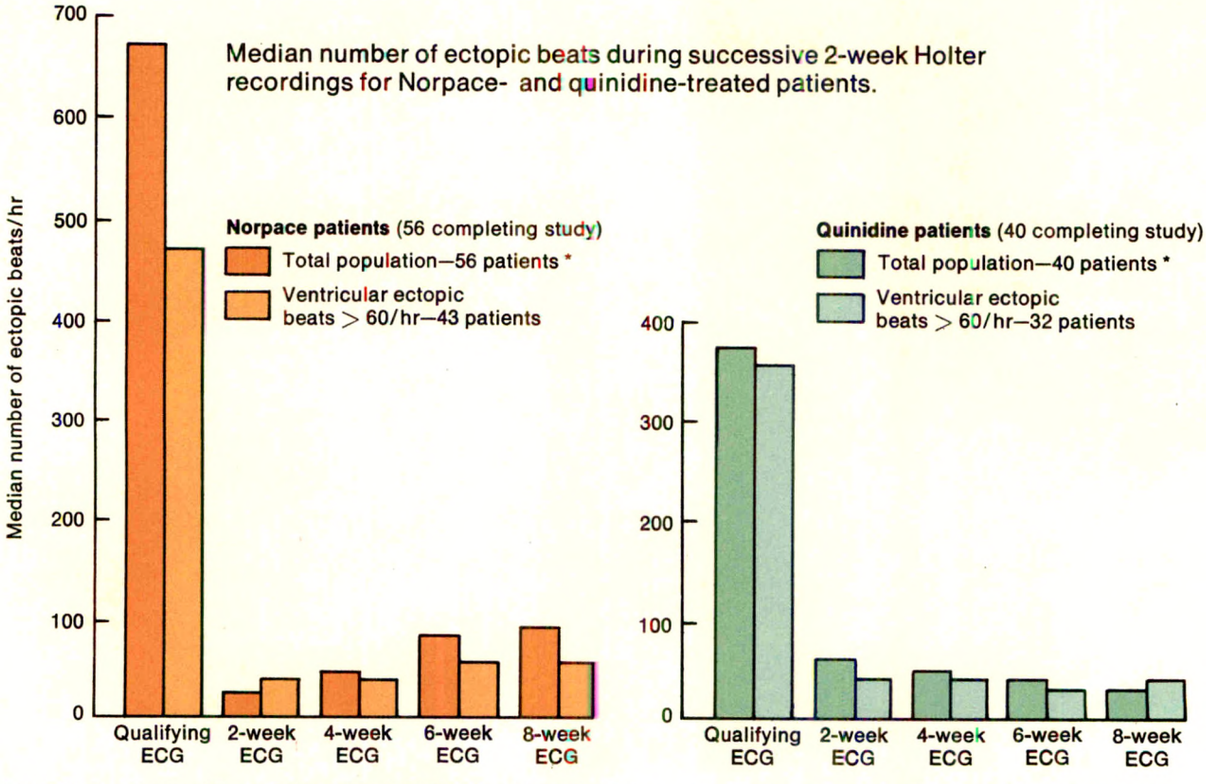
(disopyramide phosphate)

as effective as quinidine sulfate... with a

Results of double-blind controlled studies

A double-blind multicenter clinical study involving five investigators was conducted to compare the relative effectiveness and tolerance of Norpace and quinidine sulfate. Prior to qualifying for the study, each patient had antiarrhythmic medication discontinued for at least one week. Nine-hour Holter recordings were then used to establish an admission criterion of at least 60 ectopic beats per hour (PVCs, PACs or combination of the two). All other arrhythmias were excluded except paroxysmal ventricular or atrial tachycardias occurring in conjunction with the above. It was apparent that both drugs were capable of reducing ectopic activity and maintaining suppression throughout the course of therapy.

Median number of ectopic beats during successive 2-week Holter recordings for Norpace- and quinidine-treated patients.



* Includes patients with more than 60 total (atrial and ventricular) ectopic beats per hour but who had fewer than 60 ventricular ectopic beats per hour.

There was no statistically significant difference in reduction of ectopy between the two drugs.

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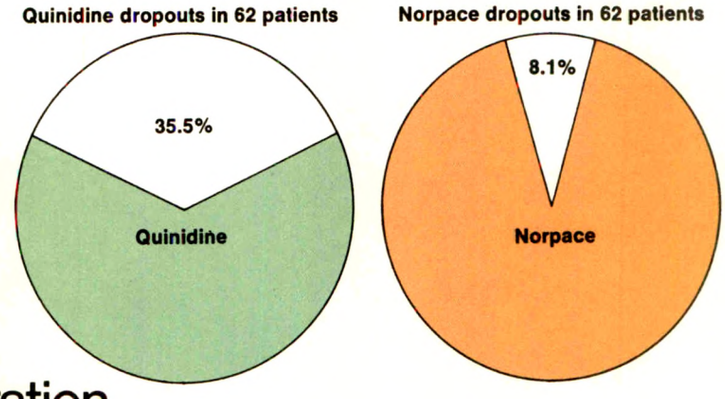
effective by extensive Holter monitoring

lower incidence of severe side effects

Significantly fewer dropouts with Norpace

(disopyramide phosphate)

The entire study population was analyzed for side effects. The side effects experienced by Norpace patients were usually mild and mainly anticholinergic, including: dry mouth, urinary hesitancy, constipation, blurred vision. The anticholinergic side effects were generally transient. Adverse reactions with quinidine were more serious and affected a greater number of patients. The most common symptoms were: severe diarrhea; gastrointestinal symptoms including cramps, nausea and vomiting; dizziness; fever; and rash.



Dosage and administration

Supplied as 100-mg and 150-mg capsules. Dosage should be individualized based on response and tolerance. Usual adult dosage is 400 to 800 mg per day given in divided doses four times daily.

Initial Norpace dosage

Patients 110 lb and over	150 mg q 6 h
Patients less than 110 lb	100 mg q 6 h
Patients with specific complications: Patients with *possible cardiac decompensation, cardiomyopathies, reduced left ventricular function* or *hypotension* due to these or other causes	100 mg q 6 h
Patients with moderate renal ($C_{cr} > 40$ ml/min) or hepatic insufficiency	100 mg q 6 h (200-mg loading dose optional)
Patients with severe renal insufficiency ($C_{cr} < 40$ ml/min)	100 mg given approximately every half-life (T½) (200-mg loading dose optional)
C_{cr} = 40–15 ml/min	q 10 h
C_{cr} = 15– 5 ml/min	q 20 h
C_{cr} = 5– 1 ml/min	q 30 h
In patients *without the complications* specified above in whom rapid control of arrhythmias is essential, therapy may be initiated with a loading dose of 300 mg (200 mg for patients under 110 lb).	

For complete Norpace dosage recommendations, please see full prescribing information, a brief summary of which appears on the next page.

SEARLE

Norpace®
(disopyramide phosphate)

as effective as quinidine sulfate for specific ventricular arrhythmias... with a lower incidence of severe side effects

Before prescribing Norpace (disopyramide phosphate), please consult current complete prescribing information, a summary of which follows:

Indications: Norpace is indicated for suppression and prevention of recurrence of the following cardiac arrhythmias when they occur singly or in combination: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion).

Norpace is equally effective in treating the above arrhythmias in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease. Oral Norpace has not been adequately studied in patients with acute myocardial infarction or in patients with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established.

Contraindications: Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug.

Warnings: Severe hypotension has been observed primarily in patients with primary cardiomyopathy or inadequately compensated congestive heart failure. If hypotension develops Norpace should be discontinued promptly unless hypotension is due to the arrhythmia.

Norpace should not be used in the presence of poorly compensated or uncompensated congestive heart failure unless it is exacerbated by or caused by an arrhythmia and proper treatment including optimal digitalization has been accomplished. In some patients with marginally compensated heart failure, Norpace may worsen cardiac decompensation. In these patients, progressing congestive heart failure should generally be treated with cardiac glycosides and diuretics and the course of treatment closely followed. Norpace dosage should be reduced or discontinued if adequate control of congestive failure is not attained.

If first-degree heart block develops, the dosage of Norpace should be reduced. If the block persists, continuation of Norpace must depend upon an assessment of the benefit versus the risk. Development of second- or third-degree AV block or uni-, bi- or trifascicular block requires discontinuation of Norpace, unless the ventricular rate is adequately controlled by a pacemaker.

Because of its anticholinergic properties, Norpace should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken.

Precautions: If significant widening (greater than 25%) of the QRS complex occurs, Norpace should be discontinued. If Q-T prolongation greater than 25% occurs and if ectopy continues, monitor closely and consider discontinuing Norpace.

Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits.

The effect of Norpace is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block.

Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of Norpace (disopyramide phosphate).

Norpace should be administered cautiously to patients who are receiving or who have recently received other antiarrhythmic drugs. Excessive widening of the QRS complex and/or prolongation of the Q-T interval may occur in such instances.

Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage.

Antiarrhythmic drugs may be ineffective in patients with hypokalemia. Therefore, any potassium deficit should be corrected before instituting Norpace therapy.

Use in Pregnancy and Lactation: Safe use in pregnancy has not been established. Norpace has been reported to stimulate contractions of the pregnant uterus. The use of Norpace in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus.

It is not known whether disopyramide is excreted in human milk. However, studies in rats have shown that the concentration of disopyramide and its metabolites is up to three times greater in milk than in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted.

Labor and Delivery: The effects of Norpace on the fetus during delivery or on the course of labor and delivery are unknown.

Pediatrics: The safety and effectiveness of Norpace in children have not been established.

Adverse Reactions: *Anticholinergic:* dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention. *Genitourinary:* urinary frequency and urgency. *Gastrointestinal:* nausea, pain/bloating/gas, anorexia, diarrhea, vomiting. *General:* nervousness, dizziness, general fatigue/muscle weakness, headache, malaise. *Cardiovascular:* hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain. *Dermatologic:* generalized rash/dermatoses. The following have occurred, but a causal relationship is uncertain: impotence, depression, insomnia, hypoglycemia, dysuria. Acute psychosis and cholestatic jaundice, both reversible, have been reported.

Dosage and Administration: Dosage must be individualized for each patient on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg per day given in divided doses four times daily. The recommended dosage schedule for most adults is 150 mg every six hours. For patients weighing less than 110 pounds (50 kg) the recommended dosage is 100 mg every six hours.

If rapid control of arrhythmia is essential, an initial loading dose of 300 mg of Norpace (200 mg for patients weighing less than 110 pounds) is recommended. For patients with cardiomyopathy or possible cardiac decompensation, a loading dose should not be given and the initial dose limited to 100 mg every six hours, with subsequent dosage adjustments made gradually under close monitoring.

See current complete prescribing information for dosage recommendations.

How Supplied: Capsules containing 100 mg or 150 mg of disopyramide base. Available in bottles of 100 capsules.

SEARLE

Searle Laboratories
Division of G. D. Searle & Co.
Box 5110, Chicago, Illinois 60680

8N-R2

HOW TO BUY AN INTEGRATED STRESS TEST SYSTEM THAT WON'T RUIN YOUR BUDGET!

from the people who designed the Quinton Treadmill!

QUINTON INSTRUMENT CO.

YOU CAN'T BEAT THE SYSTEM!

BUY IT FROM THE PEOPLE WHO BROUGHT REPEATABILITY AND PRECISION TO STRESS TESTING

...the people who designed the unbeatable system!

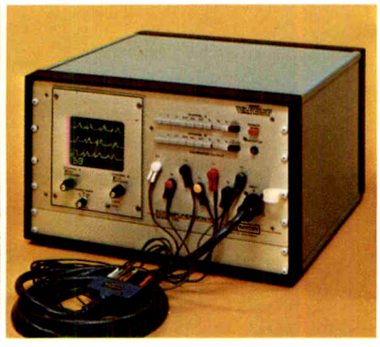
The name Quinton has long been the hallmark in the design and manufacture of treadmills for use in controlled exercise. Now, with the Model 633 three channel stress test monitor, Quinton offers a total system to make controlled stress testing accurate, repeatable and economical.

The Quinton system makes it possible for a stress testing laboratory, clinic or hospital to initiate a sophisticated test program with a moderate investment.

The Quinton system includes a time-tested Quinton Treadmill. There is a model available for virtually every application — all featuring the Quinton-pioneered endless nylon belt and "no-jerk" speed control. The treadmill is teamed with the Model 633 stress test monitor, with its advanced standard features and "plug-in" options. Together, they create the unbeatable system!

FEATURES OF THE MODEL 633

- Three channel non-fade scope with write-from-memory capability
- Three channel ECG recorder with continuous output for signal analysis
- Automatic 12-lead rotation for testing ECGs
- Low noise, shielded patient cable for optimum results during exercise
- Scope displayed digital heart rate meter
- Plus a sturdy, attractive control console which provides room to expand test capabilities with easy "plug-in" optional features such as ECG data computer... S-T computer... defibrillator...and automatic exercise control programmer which regulates both slope and speed automatically to meet your protocol needs.



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YOU CAN'T BEAT THE SYSTEM

78-2

Sir Isaac Newton's gift was the rare ability to question, to envision, and to apply...

That same special ability has brought Intermedics to the forefront of pacemaker technology.

Sir Isaac Newton's introduction of the concept of gravity immensely enriched man's understanding—and control—of his world. Similarly, the CyberLith pulse generator gives you, the physician, unprecedented control of pacemaker therapy for the individual patient. With the CyberLith, pacemaker functions can be adjusted *precisely* and titrated to an exact prescription for each patient.

The CyberLith offers:

- *15 pacing rates*
- *15 pulse widths*
- *7 sensitivity levels*
- *3 operating modes plus advanced telemetric circuitry for detailed, non-invasive performance monitoring.*

Maximum responsiveness to varying patient needs with fifteen pacing rates.

The CyberLith pulse generator can be programmed to a pacing rate appropriate to virtually any pacemaker patient case. Your patients are individuals with individual pulse rate requirements that can and do change with time. The CyberLith pacemaker's fifteen rates, from 30 to 120 bpm, offer you maximum versatility in meeting individual patient needs.

Vital flexibility with a range of fifteen pulse widths.

A choice of pulse widths from 0.15 to 2.29 msec assures effective pacing for each patient. Variations in optimal pulse width may occur as a result of the change from acute to chronic stimulation threshold levels. Other variations may be due to myocardial fibrosis, drug therapy regimens, or electrode type and position. With the CyberLith, battery longevity can be maximized through selection of the shortest pulse width needed to ensure adequate capture.

"Fine-tuning" control with a choice of seven sensitivity levels.

The CyberLith makes possible precise sensitivity adjustments in response to different clinical situations. For example, if T-waves or other artifacts are being sensed to the detriment of proper system functioning, the CyberLith pacemaker's sensitivity can be reduced to a more desirable level. Conversely, inadequate or inconsistent sensing of the QRS complex may be corrected by increasing the programmed sensitivity.

Unique versatility: three pacing modes.

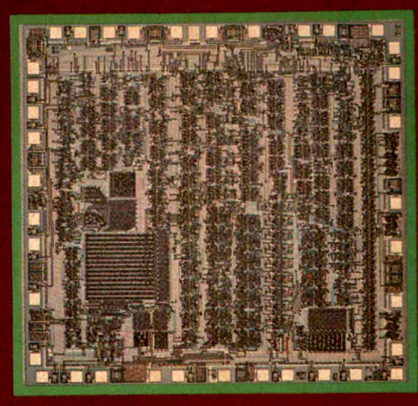
The CyberLith may be programmed to the mode best suited to your patient's condition and environment. You may choose among three pacing modes:

—R-wave inhibited (demand)
—asynchronous (fixed-rate)
—R-wave synchronous (demand)

Thus the CyberLith may be reprogrammed in response to indications for a different pacing mode, without the need for surgical intervention.

Telemetric communication with the implanted pacemaker system.

The CyberLith pacemaker's exclusive telemetry feature permits you to ascertain the precise status of the implanted



Intermedics' custom complementary metal oxide semiconductor integrated circuit magnified approximately 11 times.

Actual size of c-mos "chip" as it is employed in the CyberLith.

system to a degree never before possible.

—battery voltage
—battery impedance
—electrode lead impedance
—exact timing of sensing *and* pacing events

can all be determined simply, for detailed evaluation of pacer operations. In addition, CyberLith telemetry makes possible more accurate estimation of the remaining service life of the unit.

Big features in a small package, through microminiaturized circuitry.

The CyberLith packs a multiplicity of programming features into a remarkably small pulse generator. One reason this can be achieved is the use of a custom complementary metal-oxide-semi-conductor (c-mos) integrated circuit. This "chip" has been specially developed by Intermedics for use in the CyberLith and represents state-of-the-art semiconductor technology. The c-mos circuitry reduces the total number of components and simplifies the design of the CyberLith. The result is an unprecedented range of programmable pacing parameters with remarkably low power consumption.

Fail-safe programming at your fingertips.

Advanced design concepts have been incorporated into the programming system to ensure *safe, trouble-free operation.*

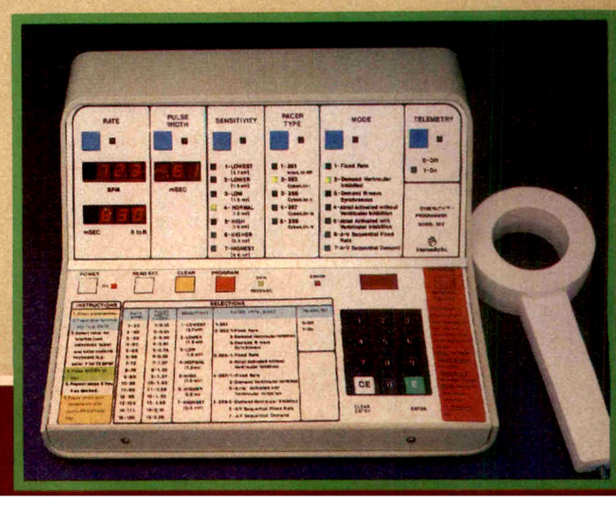
—The programmer is portable and uses rechargeable batteries to prevent unwanted electrical noise and other complications common to line-powered instruments.
—Programmable features may be altered individually or simultaneously.
—Accidental reprogramming is virtually impossible, thanks to the precise state-of-the-art crystal oscillator technology in combination with pulse-position-modulated, binary coded data security.
—A unique feature permits immediate reprogramming to *original nominal pacer parameters* by depressing a single button on the programmer panel.

These characteristics make the CyberLith programming system easy to use, and provide an added margin of safety for you and your patient.

The CyberLith—it's making history. Now.

Your Intermedics representative can provide you with additional information on the many other advantages of CyberLith therapeutic pacing, such as amazingly compact size, redundant oscillator circuitry and *positive confirmation of reprogramming.*

At Intermedics, we are producing tomorrow's technology today, because OUR BUSINESS IS LIFE.



Free limited-edition print offer from Intermedics, Inc.

The Newton watercolor, by artist Ron Adair, is first in a series commissioned by Intermedics. The original work hangs in Intermedics' corporate headquarters. A limited-edition print, numbered and signed by the artist and suitable for framing, is being made available by Intermedics to physicians only. Please write to Marketing Administration, Intermedics, Inc., P.O. Box 617, Freeport, Texas 77541.

Note: The CyberLith is currently undergoing clinical evaluation and is not routinely available on a commercial basis.

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CyberLith is a trademark of Intermedics, Inc., Freeport, Texas.

Intermedics Pulse Generators

INDICATIONS FOR USE Implantable cardiac pulse generators may be indicated for long-term treatment of impulse formation or conduction disorders resulting in symptomatic bradyarrhythmias, tachyarrhythmias, and heart block unresponsive to drug therapy.

PRECAUTIONS Implanted pacemakers have a finite and relatively widely variable service life as a result of factors such as the initial capacity of the battery and the shelf storage time of the manufactured pacemaker; variations in electrode system resistances, stimulation rate, and the percentage of time the implanted pacemaker is inhibited; and random electronic component failures.

Pacemaker operation can be influenced by electric, magnetic, or electromagnetic energy mimicking normal cardiac activity. In addition, certain environmental sources can couple sufficient energy into a pacemaker system to damage the pulse generator. Specifically, diathermy should not be used on pacemaker patients because of possible total inhibition of the pulse generator; electrocautery can inhibit and/or damage the pacemaker as well as cause burns or possible ventricular fibrillation; defibrillation can damage the pacemaker, and the presence of the pacemaker may cause increased cardiac muscle damage from defibrillation. Microwave ovens that do not exceed federal guidelines for leakage (0.5 mW/cm^2 at 2.5 cm from the appliance) will not affect the pacemaker, but leakage in excess of that amount may cause interference. Certain electrical and gasoline-powered appliances can cause inhibition of an implanted cardiac pacemaker system.

For complete precautions, see the Physician's Manual for the Intermedics cardiac pulse generator to be used.

CONTRAINDICATIONS AND SIDE EFFECTS There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. Body rejection phenomena, local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

Intermedics Inc.
P.O. Box 617 Freeport, Texas 77541
Tel: (713) 233-8611

Our business is life.

4 critical criteria in choosing a Holter service

Before you select a Holter service, make sure it meets these 4 important standards. Telemed does!

1. Technician Specialization.

Scanning a long term ECG tape is a specialty requiring intense concentration.

Telemed makes sure this concentration is not disturbed. Holter monitoring is the only responsibility our Holter technicians have. This not only sharpens their focus, but also better enables them to spot meaningful events, morphologic changes, arrhythmias, even slight abnormalities.

2. Non-Fatiguing Technician Workload.

Volume is important to any Holter scanning service, but Telemed never puts quantity ahead of quality. Telemed's "Always Alert" Policy limits the number of tapes a Holter technician can scan per day. This minimizes fatigue, so technicians are more alert, ready to recognize changes no matter how slight.

3. Emergency Alert.

Telemed provides a double assurance that you are notified immediately if any life threatening abnormalities appear. Double assurance because both the Holter technician and a staff cardiologist review each scan for events which require your immediate attention. You are notified at once when such events are spotted.

4. Continuous Dual-Channel Equipment.

The Telemed Holter Scanning Service features state-of-the-art, continuous dual-channel monitoring equipment for greater reliability in arrhythmia detection and in the diagnosis of coronary artery disease.

Telemed's Holter Scanning Service includes tapes, patient diaries, mailers, service and maintenance. Plus Telemed trains your personnel at no extra charge. For full details on how Telemed Holter Scanning can help you help your patients, call or write Telemed today.

Telemed's Holter Scanning Service meets all four crucial standards.

TELEMED®
CORPORATION

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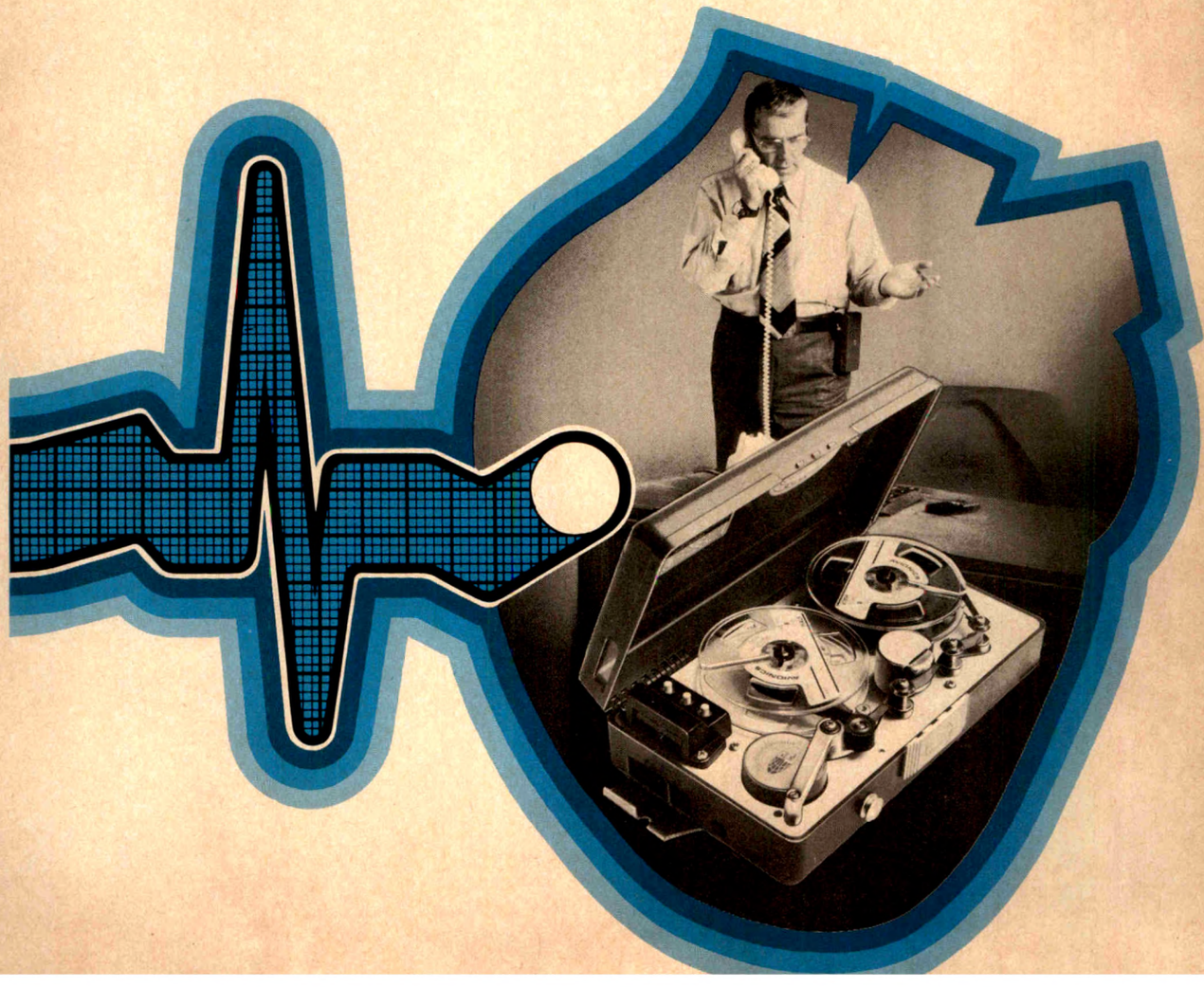
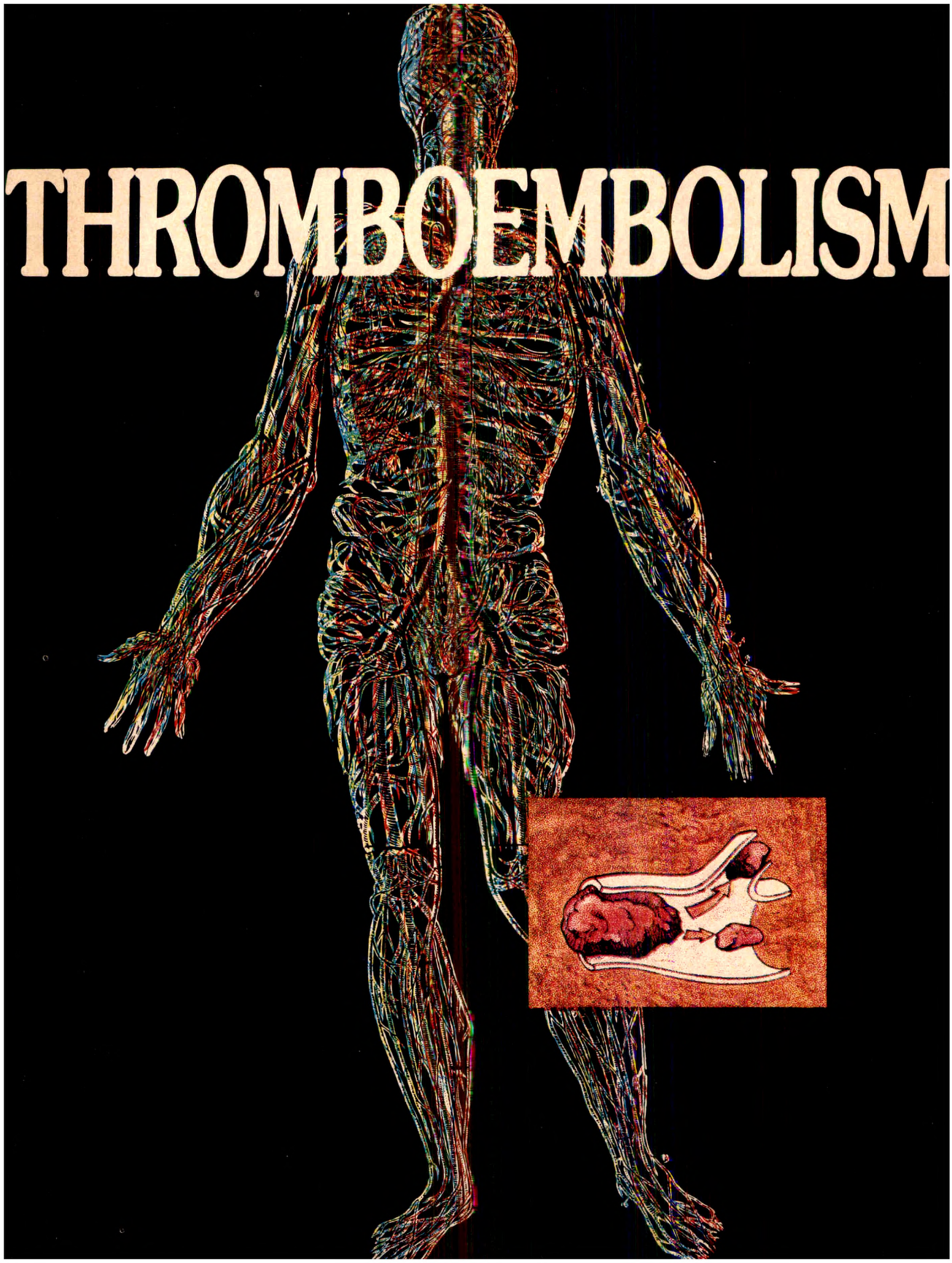
312/884-5900



THROMBOEMBOLISM



COUMADIN® (CRYSTALLINE SODIUM WARFARIN U.S.P.)

FOR ORAL ANTICOAGULATION

Prophylactic Use

A number of cardiac syndromes can predispose patients to thromboembolic episodes. The greatest threat of thromboembolism, however, exists in patients with a history of obesity, excessive cigarette smoking or previous episodes of venous thrombosis or pulmonary embolism. Postoperative patients requiring extended immobilization and the elderly are at high thromboembolic risk as are the severely injured—particularly those over 40 years with fractures of the hip, pelvis or lower extremities—and patients undergoing elective cup arthroplasty or pelvic surgery.

Emphasis should be placed on prophylaxis for those patients predisposed to thromboembolism. The oral anticoagulant of choice is COUMADIN® (crystalline sodium warfarin U.S.P.)

Therapeutic Use

For established thromboembolism, administration of I.V. heparin followed by oral anticoagulant therapy is a cornerstone of treatment. COUMADIN,® a chemically pure oral anticoagulant with high predictability of response, is a mainstay of effective therapy.

Dosage and Administration

In patients receiving COUMADIN,® prothrombin time should be maintained at 1.5 to 2.5 times the control until results stabilize. Dosage and administration should be individualized according to prothrombin time results and reevaluated periodically throughout therapy.

Patients should be well informed about their condition and medication, since factors such as dietary change, travel, other medication, change in physical condition and abrupt environmental change may influence prothrombin time and, therefore, response to COUMADIN.®

The oral anticoagulant of choice

COUMADIN®

(CRYSTALLINE SODIUM WARFARIN U.S.P.)

Endo Laboratories, Inc.

Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

DUPONT

Before prescribing, please see prescribing information on following page.

COUMADIN® is an Endo registered U.S. trademark;
U.S. Pat. No. 3,077,481 (Reissue No. 25,866)

COUMADIN®
(CRYSTALLINE SODIUM WARFARIN*)

DESCRIPTION COUMADIN® (crystalline sodium warfarin), a prothrombinopenic anticoagulant, is chemically crystalline sodium warfarin isopropanol clathrate. The crystallization of sodium warfarin virtually eliminates trace impurities present in amorphous sodium warfarin, thus achieving a crystalline product of the highest purity. Warfarin* is the coined generic name for 3-(α-Acetonylbenzyl)-4-hydroxycoumarin. On a dose-for-dose basis, COUMADIN® (crystalline sodium warfarin) is therapeutically equivalent to amorphous sodium warfarin.

ACTIONS COUMADIN® and other coumarin anticoagulants act by depressing synthesis in the liver of several factors which are known to be active in the coagulation mechanisms in a variety of diseases characterized by thromboembolic phenomena. The resultant **in vivo** effect is a sequential depression of Factors VII, IX, X and II. The degree of depression is dependent upon the dosage administered. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombosis has occurred, anticoagulant treatment aims to prevent further extension of the formed clot and prevents secondary thromboembolic complications which may result in serious and possible fatal sequelae.

After oral administration, absorption is essentially complete, and maximal plasma concentrations are reached in 1 to 9 hours. Approximately 97% is bound to albumin within the plasma. COUMADIN® usually induces hypoprothrombinemia in 36 to 72 hours, and its duration of action may persist for 4 to 5 days, thus producing a smooth, long lasting response curve. Little is known of the metabolic pathways involved in the biotransformation of oral anticoagulants in man. However, their metabolites appear to be eliminated principally in the urine.

INDICATIONS Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN® is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Pregnancy—COUMADIN® (crystalline sodium warfarin) is contraindicated in pregnancy because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy. Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms–cerebral, dissecting aorta; (4) pericarditis and pericardial effusions; (5) subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis; or lack of patient cooperation. **Spinal puncture** and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding. **Miscellaneous:** polyarthritis, vitamin C deficiency, major regional, lumbar block anesthesia and malignant hypertension.

WARNINGS Sodium warfarin is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN® are given together, a period of 4 to 5 hours should elapse after the last intravenous dose and 12 to 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when sodium warfarin is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:
Lactation–coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Prolonged dietary deficiency** (cachexia, vitamin K). **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**–sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, menometrorrhagia, allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN®, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN*.

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders–infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency–steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cinchophen; clofibrate; COUMADIN® overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon, hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methyldopa; methylphenidate; metronidazole; monoamine oxidase inhibitors; nalidixic acid; oxolinic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates; sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; trimethoprim/sulfamethoxazole; unreliable prothrombin time determinations.

†Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN® underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN®. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN® (crystalline sodium warfarin) include:

1. Minor or major hemorrhage from any tissue or organ–which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and an extremely rare reaction consisting of hemorrhagic infarction and necrosis of the skin.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN® patient aids are available to physicians on request.

The administration and dosage of COUMADIN® must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K dependent Factors VII, X and II. These factors, in addition to Factor IX, are affected by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN® should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic prothrombinopenia are 1½ to 2½ times the normal prothrombin time (e.g. 21 to 35 seconds, with a control of 14 seconds).

Induction–40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Maintenance–Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy–The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery–The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN® be adjusted to maintain the prothrombin time at approximately 1½ to 2 times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN* with Heparin–Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in situations of great emergency to administer sodium heparin initially along with COUMADIN®. The initial dose of heparin and injectable COUMADIN* may be administered together in the same syringe. It should be noted that heparin may affect the prothrombin time, and therefore, when patients are receiving both heparin and COUMADIN*, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, and preferably 4 to 5 hours after the last intravenous injection or 12 to 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN® (crystalline sodium warfarin), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN* may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN® administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can be obtained.

SUPPLIED Tablets: COUMADIN® (crystalline sodium warfarin). For oral use, single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white, 25 mg red. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100.

Injection: Available as single injection units of amorphous sodium warfarin lyophilized for intravenous or intramuscular use in a box of 6 units for use immediately after reconstitution. 50 mg: Unit consists of 1 vial, 50 mg; sodium chloride, 10 mg; thimerosal, 0.2 mg. pH is adjusted with sodium hydroxide; accompanied by a 2 ml ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

*Present as crystalline sodium warfarin isopropanol clathrate.

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Prolonged Protective Effect of Propranolol on Hypoxic Heart Muscle

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To assess whether the in vivo administration of propranolol protects heart muscle against the deleterious effects of hypoxia and to establish how long the protection persists after cessation of therapy, rabbits were given propranolol, 2.0 mg/kg subcutaneously twice daily for 5 to 6 days. This dose regimen was used to provide plasma levels comparable with those obtained clinically. The hearts were isolated and perfused under either aerobic (partial pressure of oxygen [PO_2] greater than 600 mm Hg) or hypoxic (PO_2 less than 6 mm Hg) conditions. Heart rate was kept constant. Coronary effluent was collected and assayed for creatine kinase (CK) activity and myoglobin content. Resting and peak systolic tension was monitored and, after 60 minutes of perfusion, the mitochondria were harvested and assayed for respiratory activity (atoms oxygen used/mg mitochondrial protein per min [QO_2], respiratory control index [RCI] and nmol adenosine diphosphate used/n atoms oxygen consumed [ADP/O_2 ratio]) and Ca^{++}-accumulating activity. The control rabbit hearts responded to the hypoxia-perfusion state with release of CK and myoglobin and an increase in resting tension. Mitochondrial QO_2 and RCI were significantly depressed. Mitochondrial Ca^{++}-accumulating activity was enhanced. The propranolol-treated rabbit hearts were protected in that they released CK and myoglobin more slowly and had a lower rate of rise of resting tension. Mitochondrial respiratory activity (QO_2 and RCI) was also better maintained, and the mitochondria accumulated Ca^{++} at a relatively slow rate. This protective effect of propranolol pretreatment was not accompanied by a changed tissue level of adenosine triphosphate, creatine phosphate or glycogen.

The protective effect of propranolol persisted for up to 72 hours after the last dose of propranolol, and hence was present when beta adrenoceptor blockade was no longer effective. These results support the hypothesis that there may be secondary consequences of beta blockade.

In previous studies,[1–3] we found that the acute in vitro administration of racemate propranolol protects adult heart muscle against some of the deleterious consequences of hypoxia. This evidence of protection was provided by reduced rates of enzyme leakage (creatine kinase [CK]),[1] a slowed rate of rise of resting tension[2] and the preservation of mitochondrial function.[3] The following experiments were undertaken to establish (1) whether a similar protective effect of propranolol can be detected after in vivo administration, and (2) how long the protection persists after cessation of therapy.

Methods

Adult (2.5 to 3.0 kg) male New Zealand White rabbits were used. The control rabbits (no. = 174) received 1 mg/kg of 0.9 percent sodium chloride solution subcutaneously, twice daily, and the others 2.0 mg/kg of racemate propranolol (no. = 288) subcutaneously, twice daily, for the same period of time.

From the Cardiothoracic Institute, University of London, London, England. This study was supported by grants from The Medical Research Council of Great Britain, London, England and The Wellcome Foundation, London, England. Manuscript received September 28, 1977; revised manuscript received February 22, 1978, accepted March 22, 1978.

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This dose regimen has been shown to provide plasma levels comparable with those observed clinically.[4] Treatment was given for 5 or 6 days to ensure effective beta adrenoceptor blockade. The rabbits used for a particular experiment were chosen at random from the treated pool irrespective, unless otherwise stated, of whether they had been treated with propranolol for 5 or 6 days.

Perfusion of hearts: The rabbits were fed as desired on a standard diet of water, cabbage leaves and Short Gamage IV diet. When required each rabbit was stunned by a blow on the head. The heart was rapidly removed and rinsed in an ice-cold modified Krebs-Henseleit buffer[5] containing (in millimolar) sodium chloride 115.0, sodium bicarbonate 25.0, potassium chloride 4.0, potassium biphosphate 0.9, magnesium sulfate 1.1, calcium chloride 1.5 and glucose 11.0, and equilibrated with 95 percent oxygen and 5 percent carbon dioxide. After the extraneous fat and connective tissue were removed, the hearts were perfused with the nonrecirculating Langendorff technique,[6] using buffer solution[5] equilibrated with 95 percent oxygen and 5 percent carbon dioxide and warmed to 37° C. The buffer solution was delivered to the aortic cannula[7] by means of a two-way stopcock at a perfusion pressure of 60 to 80 mm Hg, maintained with a Watson Marlow (MHRE MK3, Marlow, Buckinghamshire, United Kingdom) rotary pump and monitored, at the head of the aortic inflow cannula, with a Statham P23Db transducer or a pressure manometer. Cellulose acetate filters of 5.0 μmolar pore size (Milliport Ltd., Bedford, Massachusetts) were included in the perfusion line, and the ventricles were vented to prevent any accumulation of fluid.

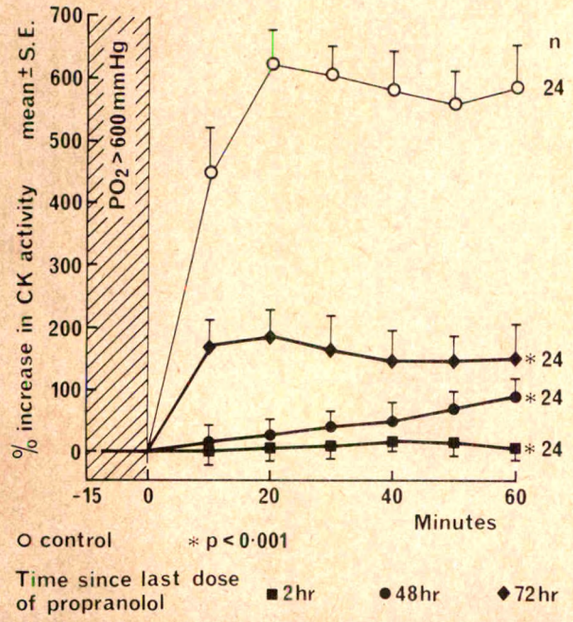

FIGURE 1. Effect of twice daily subcutaneous injections of 2.0 mg/kg of propranolol for 5 or 6 days on hypoxia-induced release of creatine kinase (CK) in rabbit hearts. Each point is the mean ± standard error (S.E.) of n experiments. The animals were killed 2, 48 or 72 hours after the last injection. The hearts were paced at 140 beats/min, and the percent increase in CK release was calculated with respect to the release that occurred during the preliminary period of aerobic perfusion. Hypoxic conditions were introduced after the hearts had been perfused aerobically (PO_2 greater than 600 mm Hg) for 30 minutes. Control refers to rabbits treated with saline solution (see text). n = number of experiments; p = probability.

The hearts were paced[1] at 140 beats/min, using suprathreshold rectangular pulses of 1.0 msec duration delivered from a Tektronix square wave generator assembly by means of two electrodes, one attached to the metal inflow cannula and the other to the ventricular apex.

Tension development was monitored as previously described[2] with a Grass FT03 transducer attached by a nylon ligature to the ventricular apex. The output from the transducer was displayed on a Devices direct writing recorder (MX 212) at a paper speed of 1 mm/sec. At the start of each experiment resting tension was adjusted until the developed tension reached its peak. This involved applying a resting tension of 2.86 ± 0.3 g (mean ± standard error of the mean, 78 experiments). The increase in resting tension (described later) was calculated as the difference between the resting tension developed after a given period of time and this preset tension. The difference between the resting and peak developed tension is referred to as peak systolic tension.

After 30 minutes of perfusion with Krebs-Henseleit buffer solution gassed with 95 percent oxygen + 5 percent carbon dioxide (aerobic perfusion PO_2 greater than 600 mm Hg, measured with a Radiometer O_2 electrode, type E5046, Radiometer, Copenhagen, Denmark), the hearts were randomly divided into two groups. The hearts in one group were perfused as described with aerobic Krebs-Henseleit solution (PO_2 greater than 600 mm Hg) for another 60 minutes. The hearts in the second group were perfused as described for another 60 minutes, but using hypoxic (PO_2 less than 6 mm Hg) substrate-free Krebs-Henseleit solution prepared by substituting mannitol for glucose and gassing with 95 percent nitrogen and 5 percent carbon dioxide instead of 95 percent oxygen and 5 percent carbon dioxide.

Coronary effluent analysis: During the 90 minutes of each perfusion (30 minutes of equilibration followed by 60 minutes of experimental period), the coronary effluent was collected by timed collection into chilled glass vials and assayed, on the same day, for creatine kinase (CK) activity[7] and myoglobin content. CK activity was measured spectrophotometrically with a modification[8] of the method described by Oliver.[9] The myoglobin in the coronary effluent was assayed spectrophotometrically, at 410 nanometers.

Mitochondrial function studies: At the end of some of the perfusion periods, the hearts were homogenized and their mitochondria harvested by homogenization and differential centrifugation as described by Sordahl et al.[10] The composition of the mitochondrial pellets was checked with electron microscopy, enzyme studies and, as previously described,[3] by repeated additions of adenosine diphosphate (ADP) during incubation at either 25° or 37°, as indicated by Lindenmayer et al.[11] The oxidative phosphorylating activity of the mitochondria was monitored polarographically (at 25° C) using a Clark O_2 electrode. The incubation medium contained 125.0 millimolar potassium chloride; 12.5 millimolar Tris-HEPES (N-2-hydroxethylpiperazine) N′-2-ethanesulfonic acid) buffer, pH 7.2; 3.0 millimolar Tris pyruvate or glutamate (as substrate); 3.0 millimolar potassium biphosphate; 0.5 millimolar ethylenediamine tetraacetic acid (EDTA); 2 percent dextran, 0.75 mg mitochondrial protein/ml and 0.25 millimolar ADP. Mitochondrial function was monitored[3] in terms of the ADP/oxygen ratio (nanomoles ADP used/n atoms oxygen consumed); QO_2 (n atoms oxygen used/mg mitochondrial protein/min) and RCI (respiratory control index, the ratio of oxygen used in the presence of ADP to that taken up after phosphorylation to ATP). Protein was determined by the Lowry method.[12] The Ca^{++}-accumulating activity of the mitochondria was monitored[3] using a DW 2 Aminco Bowman spectrometer at 507 to 542 nanometers and a reaction mixture

containing 150.0 millimolar sucrose; 75.0 millimolar potassium chloride; 2.0 millimolar potassium bisulfate; 3.0 millimolar Tris hydrochloric acid (pH 7.2); 5.0 millimolar magnesium chloride; 1.7 millimolar sodium succinate; 35.0 millimolar murexide; 3.9 micromolar rotenone; 10 to 100 micromolar Ca^{++} and 250 to 300 micrograms mitochondrial protein/ml.[13] These Ca^{++}-accumulation studies were performed at 37° C and the mitochondria, unlike those used for the phosphorylation studies, were resuspended before use in an EDTA-free solution containing 180 millimolar potassium chloride and 0.5 percent bovine serum albumin.

Tissue CK and wet weight/dry weight analysis: To interpret the data from the CK release studies (Fig. 1), we needed to establish if propranolol pretreatment alters the total CK activity of the heart. To do this we used the extraction procedure described by Hearse and Humphrey[14] based on that of Sobel et al.[15] Briefly, the hearts were excised, weighed and perfused for 30 minutes as described, using standard aerobic buffer with glucose. After a small sample of left ventricular wall (0.05 g) was taken for wet/dry weight analysis, the hearts were freeze-clamped (between stainless steel tongs precooled in liquid nitrogen) and powdered in a chilled percussion mortar. The resultant powder was homogenized, extracted[14] and assayed, together with the coronary effluent, for CK activity.[8,9] The tissue sample was dried at 100° C to constant weight, for the dry weight determination.

Adenosine triphosphate (ATP), creatine phosphate and glycogen determinations: Because the hearts excised from the propranolol-treated rabbits were protected against the deleterious effects of hypoxia being studied (Fig. 1 to 6) and because this protection persisted after the beta blocking properties of propranolol had disappeared, we examined whether the prolonged protection was accompanied by raised tissue levels of ATP, creatine phosphate or glycogen. The hearts used for this purpose were perfused aerobically, as described, for 30 minutes. This schedule was adopted so that the ATP, creatine phosphate and glycogen content of the muscle would be measured when the hypoxia-perfusion conditions had been introduced.

The perfusion of hearts in which ATP, creatine phosphate and glycogen levels were to be measured was terminated by freeze-clamping the hearts between large stainless steel tongs precooled in liquid nitrogen. The frozen ventricular muscle was powdered in a percussion mortar maintained at a temperature of liquid nitrogen. Approximately 200 mg of the frozen muscle was immersed in a precooled, preweighed tube containing 6 percent (volume for volume) perchloric acid and assayed for ATP and creatine phosphate, as described by Opie et al.,[16] and for glycogen, as described by Bergmeyer.[17]

Reagents: Analytical reagent grade chemicals were used for the Krebs-Henseleit buffer solution, which was freshly prepared daily. Racemate propranolol was obtained from

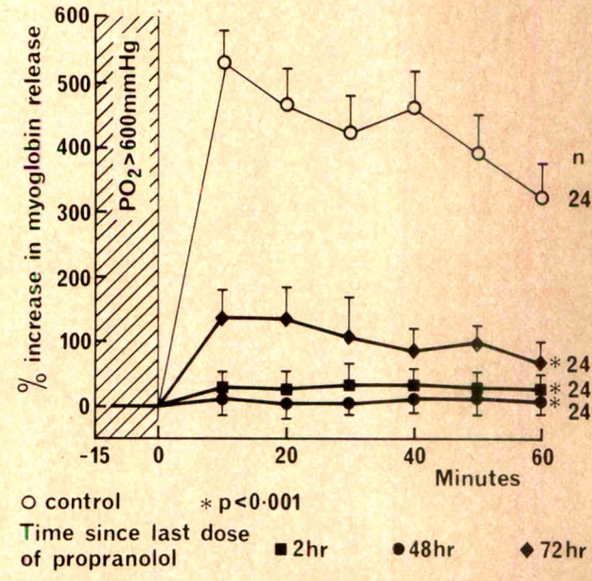

FIGURE 2. Effect of twice daily subcutaneous injections of 2.0 mg/kg of propranolol for 5 or 6 days on hypoxia-induced release of myoglobin into the coronary effluent. The conditions of the experiment are as described for Figure 1. n = number of experiments; p = probability.

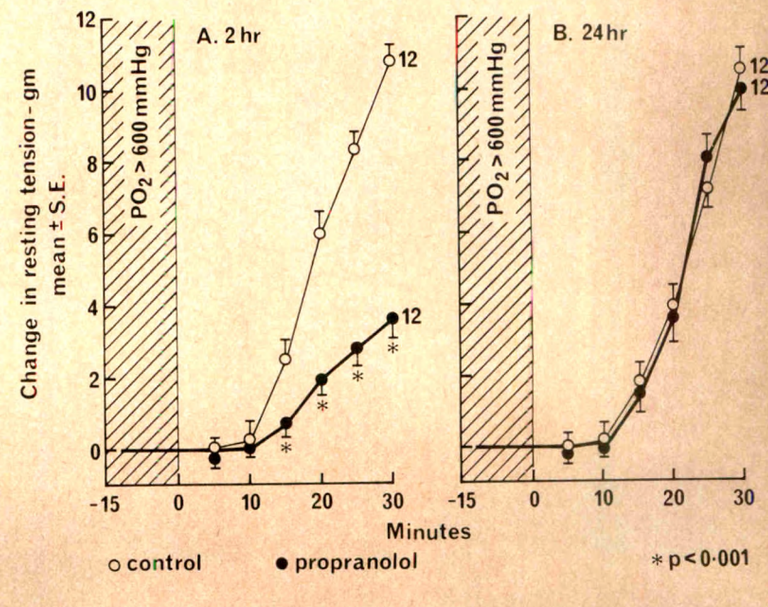

FIGURE 3. Effect of twice daily subcutaneous injections of 2.0 mg/kg of propranolol on the increase in resting tension induced by hypoxia. The rabbits were killed either 2 **(A)** or 24 **(B)** hours after the last dose of propranolol had been given. Each point indicates the mean ± standard error (S.E.) of 12 experiments. The hearts were electrically paced (140 beats/min), and the change in resting tension caused by the hypoxia was calculated relative to the resting tension developed during the preliminary period of aerobic perfusion. Hypoxic (PO_2 less than 6 mm Hg) conditions were introduced at 0 on the time scale after 30 minutes of aerobic perfusion. Control refers to rabbits pretreated with saline solution. p = probability.

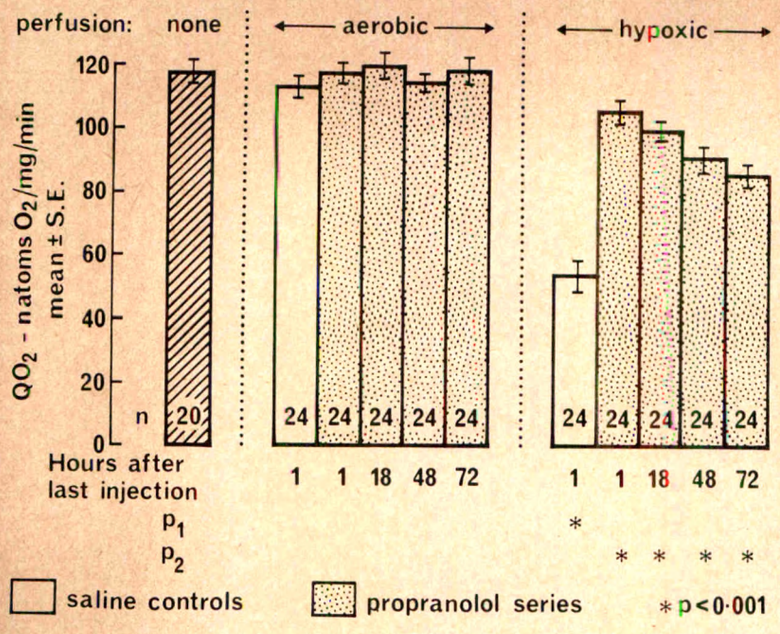

FIGURE 4. Effect of twice daily subcutaneous injections of 2.0 mg/kg of propranolol for 5 to 6 days on hypoxia-induced changes in mitochondrial QO_2 (n atoms oxygen used/mg mitochondrial protein per min). Except for the 20 nonperfused hearts **(first bar)**, the hearts that were isolated from these pretreated animals were perfused aerobically for 30 minutes and then under aerobic or hypoxic and substrate-free conditions for 1 hour before the mitochondria were isolated. Propranolol was not added to the perfusion circuit. P_1 tests of significance relate to the significance of the change in QO_2 caused by the hypoxic perfusion, and the P_2 values to the significance of the protection resulting from the prior treatment with propranolol. The QO_2 activity was measured as described in the text, using Tris-pyruvate or glutamate as substrate. p = probability; S.E. = standard error of the mean.

Imperial Chemical Industries and isoproterenol sulfate from Burroughs Wellcome, England.

Statistics: Results were expressed as mean ± standard error of the mean of n experiments, and the statistical significance of differences was calculated with Student's t test, taking $P = 0.05$ as the limit of significance.

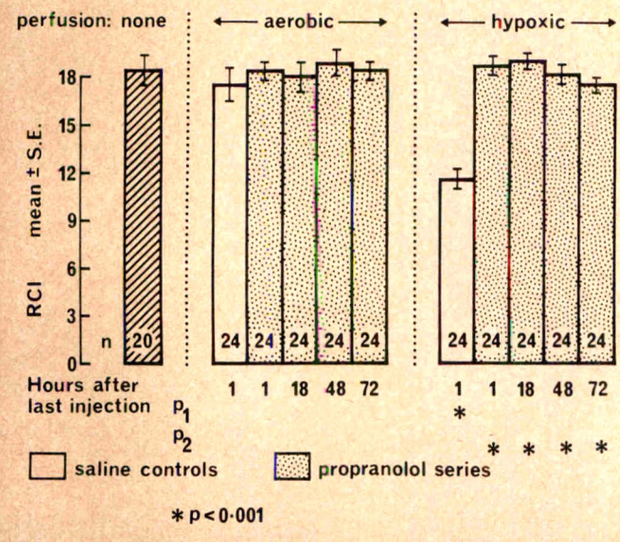

FIGURE 5. Effect of twice daily subcutaneous injections of 2.0 mg/kg of propranolol for 5 to 6 days on hypoxia-induced changes in mitochondrial respiratory control index (RCI). The hearts that were isolated from these pretreated rabbits were perfused as described for Figure 4. Propranolol was not added to the perfusion circuit. P_1 tests of significance relate to the significance of the change in RCI caused by the hypoxic perfusion, and the P_2 values to the significance of the protection resulting from prior treatment with propranolol. n = number of separate experiments made under the relevant conditions of perfusion; p = probability; S.E. = standard error of the mean.

Results

Creatine phosphate release: When isolated paced (140 beats/min) adult rabbit hearts are perfused under *aerobic* (PO_2 greater than 600 mm Hg) conditions for 90 minutes, only small amounts of creatine kinase (CK) appear in the coronary effluent[1] whether or not the rabbits have been pretreated with propranolol. Under these conditions of aerobic perfusion no difference ($P < 0.8$) could be detected between the amounts of CK released from the hearts of the control and the propranolol-treated rabbits. By contrast, the isolated paced (140 beats/min) control hearts equilibrated for 30 minutes with aerobic Krebs-Henseleit buffer (PO_2 greater than 600 mm Hg) and then perfused under hypoxic (PO_2 less than 6 mm Hg) substrate-free conditions released large ($P < 0.001$) amounts of CK into the coronary effluent (Fig. 1). These results resemble those previously described[1] for hypoxia-perfused rabbit hearts. However, Figure 1 shows that under hypoxic substrate-free conditions, the similar perfusion of hearts excised from rabbits killed 2, 48 or 72 hours after administration of the last dose of propranolol resulted in a slower release of CK ($P < 0.001$) than in the untreated preparations. This prolonged protection was not an artifact due to the additional days of maintenance of the rabbits because the hearts of the control rabbits injected with saline solution showed no such reduction in CK release during similar periods of perfusion under hypoxic substrate-free conditions.

Table I shows that the total CK activity extracted from the hearts was not significantly altered by 5 to 6 days of pretreatment with propranolol. The reduced CK release described in Figure 1 for the hypoxia-perfused hearts of propranolol-pretreated rabbits was therefore not due to an effect of propranolol on the total CK activity of the tissue. Nor can it be explained by different heart rates because all the hearts were paced. The tension records made during the preliminary period of equilibration in the aerobic buffer solution failed to show any significant difference between the peak systolic tension developed in the control and the propranolol-treated hearts.

Myoglobin release: Figure 2 shows that during perfusion under hypoxic substrate-free conditions, the hearts of rabbits

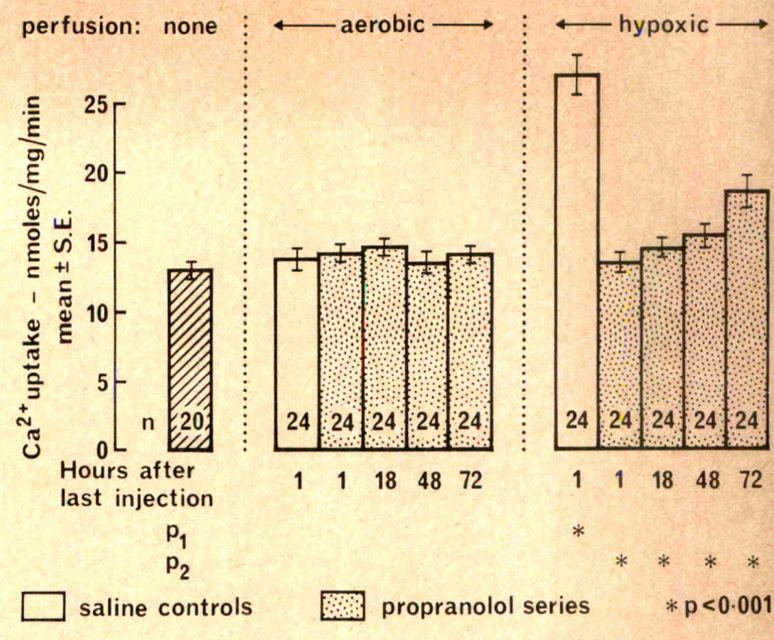

FIGURE 6. Effect of twice daily subcutaneous injections of 2.0 mg/kg of propranolol for 5 to 6 days on hypoxia-induced changes on the Ca^{++} (Ca^{2+})-accumulating activity of cardiac mitochondria. The hearts that were isolated from these pretreated adult animals either were not perfused or were perfused aerobically for 30 minutes and then under either aerobic or hypoxic conditions for 1 hour before the mitochondria were isolated and incubated at 37° C as described in the text, in the presence of 22 micromolar Ca^{++}. Propranolol was not added to the perfusion circuit. P_1 tests of significance relate to the significance of the change in Ca^{++}-accumulating activity caused by the hypoxic perfusion, and P_2 to the significance of the protection resulting from prior treatment with propanolol. n = number of separate experiments made; p = probability; S.E. = standard error of the mean.

killed 2, 48 or 72 hours after the last dose of propranolol released less myoglobin into the coronary effluent than the untreated control hearts (P <0.001). During similar periods of aerobic perfusion there was virtually no release of myoglobin into the coronary effluent (P <0.6). Other studies showed that the hearts of rabbits injected with saline solution for 5 to 6 days and then killed 2, 48 or 72 hours after the last injection released myoglobin into the coronary effluent during hypoxic substrate-free perfusion at a rate not significantly different from that shown in Figure 2 for the hypoxia-perfused untreated control rabbit hearts (P <0.8).

Resting tension: The isolated paced (140 beats/min) rabbit hearts equilibrated for 30 minutes with aerobic Krebs-Henseleit buffer manifested a constant peak systolic and resting tension when perfused aerobically for 60 minutes. However, hypoxic perfusion caused a progressive rise in resting tension (Fig. 3).

Figure 3A shows that the hearts from adult rabbits killed 2 hours after receipt of the last dose of propranolol were protected against the increase in resting tension caused by the hypoxic conditions used. Figure 3B shows that this protective effect of propranolol was no longer apparent in rabbits killed 24 hours after the last dose of propranolol. Control studies (results not shown) confirmed that, during similar periods of aerobic perfusion, resting tension of the control and propranolol-treated series remained constant (P <0.7).

Mitochondrial function: In previous studies we[3] and others[18] showed that mitochondria harvested from hearts perfused under hypoxic substrate-free conditions exhibit a depressed nanoatoms oxygen/mg mitochondrial protein per min (QO_2) and respiratory control index (RCI)[3,18] and an enhanced Ca^{++}-accumulating[3] activity. This effect of such perfusion is shown in Figures 4 to 6. These figures and Table II also show that the decline in mitochondrial QO_2 and RCI (Fig. 4 and 5) and the increase in their Ca^{++}-accumulating activity (Fig. 6) caused by the previous 60 minutes of perfusion under hypoxic substrate-free conditions of the whole heart can be prevented to some extent by pretreatment with propranolol. This protective effect persisted for as long as 72 hours after the last dose of propranolol had been given. In these experiments, the rabbits were pretreated with propranolol as described for 5 to 6 days. The hearts were then perfused aerobically for 30 minutes and then for 1 hour under either aerobic or hypoxic conditions as described. The mitochondria were isolated without the addition of propranolol to either the perfusion circuit or the isolated mitochondria.

Although pretreating the rabbits with propranolol protected the QO_2, RCI and the Ca^{++}-accumulating activity of the mitochondria isolated from hearts perfused under hypoxic conditions, it failed to affect these activities of mitochondria isolated after the same period of aerobic perfusion (Fig. 4 to 6, Table II). Aerobic perfusion also did not alter these indexes of mitochondrial metabolism. Our failure to find a significant effect of hypoxia on the mitochondrial ADP/oxygen ratio confirms our earlier results[3] and those of Lochner et al.[18,19] As discussed elsewhere[3] in detail, there are several reasons for believing that the hypoxia-induced changes in mitochondrial function in our study were not due to excessive fragmentation of the mitochondria during their isolation. Electron micrographs of the pellets consistently showed that intact mitochondria were being harvested from the aerobic and hypoxia-perfused hearts of control and propranolol-treated rabbits.[3] The field of mitochondria was approximately the same (9.0 to 11.6 mg protein/g wet weight) and, when the mito-

TABLE I

Total Creatine Kinase (CK) Activity Recovered From Fresh Rabbit Hearts (Combined Solubilized Mitochondrial and Cytoplasmic Fraction, and the Coronary Effluent)

Experiment	no. of Hearts	CK Activity (mIU/g dry weight)*
Control	4	1,316,000 ± 462
Propranolol		
5 days' treatment	4	1,462,000 ± 515
6 days' treatment	3	1,418,000 ± 215

* Mean ± standard error of the mean.

Propranolol pretreatment as described in the text (2.0 mg/kg of propranolol, subcutaneously for 5 or 6 days). The rabbits were killed 1 hour after receiving the last dose of propranolol. Control animals were treated with 0.9 percent sodium chloride, as described in the text.

TABLE II

Sequential Determinations of RCI, QO_2 and ADP/O_2 Ratios for Mitochondria from Aerobic and Hypoxia-Perfused Hearts of Control and Propranolol-Treated Rabbits

Experiment	Control Rabbit Hearts		Rabbits Treated With Propranolol for 5 to 6 Days	
	Perfusion State		Perfusion State	
Temperature 37° C	Aerobic	Hypoxia	Aerobic	Hypoxia Perfusion
RCI				
1st	16.5	12.2	16.7	16.6
2nd	16.2	11.9	16.4	16.3
3rd	16.3	11.7	16.4	16.3
QO_2				
1st	298.0	156.0	286.0	262.0
2nd	262.0	135.0	275.0	256.0
3rd	258.0	138.0	271.0	256.0
ADP/O_2				
1st	2.6	2.4	2.5	2.6
2nd	2.5	2.2	2.5	2.4
3rd	2.5	2.2	2.4	2.5
Temperature 25° C				
RCI				
1st	16.3	11.9	16.4	16.1
2nd	16.1	12.0	16.4	15.9
3rd	16.2	11.8	16.1	15.7
QO_2				
1st	118.6	49.5	121.4	98.6
2nd	120.4	47.8	117.8	98.2
3rd	115.9	48.6	118.1	97.6
ADP/O_2				
1st	2.5	2.3	2.5	2.4
2nd	2.4	2.2	2.3	2.3
3rd	2.4	2.2	2.3	2.4

The mitochondria were isolated from the hearts of two control and two propranolol-treated rabbits. The hearts from one control and one propranolol-treated rabbit were perfused aerobically (PO_2 greater than 600 mm Hg) and the hearts of the other control and propranolol-treated rabbits under hypoxic substrate-free conditions (see text). The mitochondria were incubated at 25° and 37°C for 90 minutes, while three sequential determinations of values for respiratory control index (RCI), n atoms oxygen used/mg mitochondrial protein per min (QO_2) and nanomoles adenosine diphosphate used/n atoms oxygen consumed (ADP/O_2 values) were made, using Tris-glutamate as substrate and adding ADP to provide a final concentration of 0.25 millimolar. 1st, 2nd and 3rd refer to the sequential determinations of the functions described. Note that the mitochondria for the aerobic control study came from one heart, for the hypoxia control study from another, for the aerobic propranolol study from a third heart and for the hypoxic propranolol study from a fourth heart. Three other experiments yielded comparable results.

chondria were incubated for prolonged periods at either 25° or 37° C and with repeated additions of 0.25 millimolar ADP, their respiratory activity remained stable.

The relevant data in Figures 4 to 6 show that the perfusion as such did not greatly alter the functioning of the mitochondria that were subsequently isolated. Had this been the case, we would not have expected that the mitochondria from the nonperfused hearts would have so closely resembled (in terms of QO_2, RCI and Ca^{++}-accumulating activities) the mitochondria from the aerobically perfused hearts.

The results presented in Figures 1, 2 and 4 to 6 show that hearts excised from rabbits as long as 72 hours after receipt of the last dose of propranolol are protected to some extent against the deleterious effects of hypoxia. We therefore sought to establish (1) how long effective beta blockade persisted after cessation of therapy, and (2) whether 5 to 6 days of pretreatment with propranolol had altered the cardiac stores of ATP, creatine phosphate and glycogen.

TABLE III

Duration of Propranolol-Induced Beta Blockade in Adult Rabbits

	Hours After Last Dose of Propranolol					
	0.5	1	5	18	48	72
Percent blockade	100	100	56 ± 8	4 ± 2	0	0
no. of hearts	4	4	4	4	4	4

The hearts were isolated 0.5 to 72 hours after administration of the last dose of propranolol (2.0 mg/kg subcutaneously, twice daily, for 5 days). They were stimulated electrically at 140 beats/min. Percent beta adrenoceptor blockade was calculated relative to the increase in peak tension caused by the presence of 2 μg/liter of isoproterenol in the perfusion circuit. Results are expressed as mean ± standard error of the mean for n experiments.

Duration of beta blockade: To determine how long the beta blocking properties of propranolol persisted after cessation of therapy, the hearts from adult rabbits that had been pretreated with propranolol as described for 5 or 6 days were isolated and perfused aerobically (see Methods) with a strain gauge attached to the ventricular apex. The hearts were paced at 140 beats/min, and the degree of beta blockade was established by observing the inotropic response evoked by 2 μg/liter of isoproterenol. The results obtained are summarized in Table III, in which the blockade that was evident in the hearts excised from the rabbits 30 minutes after receipt of the last dose of propranolol was taken to be 100 percent. It is evident that effective beta blockade was present 30 minutes and 1 hour but not 18, 48 or 72 hours after the last dose of propranolol had been given. The hearts used to determine the duration of beta blockade were discarded and not used for the other studies reported.

Cardiac stores of ATP, creatine phosphate and glycogen: The hearts used for the ATP, creatine phosphate and glycogen determinations were excised (Table IV) from rabbits killed 2, 24 or 48 hours after administration of the last dose of propranolol. Pretreatment of the rabbits with either saline placebo or propranolol had been continued for 5 to 6 days before the animals were killed, and the hearts were all perfused aerobically for 30 minutes before being freeze-clamped for analysis. The results, summarized in Table IV, show that the ATP, creatine phosphate and glycogen content of the muscle was the same for the control and propranolol-treated series whether 2, 24 or 48 hours had elapsed since the last dose of propranolol. The wet/dry weight ratios also remained unchanged.

Discussion

Several studies have shown that propranolol protects heart muscle against the effects of hypoxia[1,20] and ischemia.[21,22] Various techniques have been used to demonstrate this protection, including the monitoring of enzyme release patterns, measurement of changes in resting tension and mitochondrial function studies. Our results show that (1) 5 or 6 days of pretreatment with propranolol protects rabbit heart muscle against some of the deleterious consequences of hypoxia, and (2) this protection persists for as long as 72 hours after cessation

TABLE IV

Effect of 5 to 6 Days of Propranolol Pretreatment on the Cardiac Stores of Adenosine Triphosphate, Creatine Phosphate, Glycogen and the Wet/Dry Weight Ratio (mean ± standard error of the mean, n experiments)

	no. of Hearts	ATP	CP	Glycogen	Wet/Dry Weight Ratio
Control	12	16.2 ± 1.1	28.7 ± 2.2	72.3 ± 4.6	8.8 ± 0.3
2 hours*	7	15.8 ± 0.8	27.9 ± 1.2	76.7 ± 8.1	8.3 ± 0.2
24 hours*	5	16.5 ± 1.2	22.6 ± 2.1	79.5 ± 6.2	8.9 ± 0.4
48 hours*	4	16.7 ± 1.2	27.9 ± 1.3	73.2 ± 4.8	9.1 ± 0.6

* After last dose.
Adenosine triphosphate (ATP), creatine phosphate (CP) and glycogen results are expressed as μmoles/g dry weight. Tests of significance were calculated relative to the values obtained for the control series, treated only with saline placebo. There were no significant differences. All hearts used for these determinations were perfused aerobically for 30 minutes before being taken for analysis.

of therapy and thus is present at a time when effective beta blockade has disappeared. This prolonged protection resulted in reduced rates of enzyme (CK) and myoglobin release and the preservation of mitochondrial function during periods of hypoxic substrate-free perfusion. In these studies we used substrate-free conditions of hypoxic perfusion because it is well known that including or increasing the concentration of glucose in the extracellular phase protects heart muscle against the deleterious effects of hypoxia.[1,23–25]

Mechanisms of Propranolol's Protective Effect

The protection that results from 5 to 6 days' treatment of adult animals with propranolol is difficult to interpret. The protection evident in rabbits killed 1 or 2 hours after administration of the last dose of propranolol can probably be explained in terms of beta-adrenoceptor blockade. Heart muscle releases endogenous catecholamines in response to hypoxia,[26] and catecholamines increase the sensitivity of heart muscle to lack of oxygen.[27] The short duration of functional blockade we observed on cessation of treatment (no block 18 hours after the last dose) is in agreement with the evidence of Vaughan Williams et al.[4] and with the rapid disappearance of propranolol from the plasma.

Secondary effect in addition to beta blockade: The prolonged protective effect of 5 to 6 days' treatment with propranolol is difficult to explain in terms of beta blockade and presumably involves a secondary effect. There is good reason to believe that our evidence favoring the existence of a long-term protective effect of propranolol is not artifactual. The reduced rate of CK release observed was not associated with a change in the total CK activity of the heart. It is theoretically possible that pretreatment with propranolol may have altered the distribution of CK so that the size of the "pool" available for release was changed, but there is no documented evidence of this. As for the mitochondrial studies, the data obtained from the experiments in which repeated additions of ADP were made at either 25° or 37° C rule out the possibility that mitochondria extracted from the hypoxia-perfused hearts of control animals were damaged and leaked[11] more than those of the hypoxia-perfused hearts of the propranolol-treated rabbits.

Altered availability of stores of cellular energy or substrate: Five or 6 days of treatment with propranolol apparently failed to alter the ATP, creatine phosphate and glycogen content of the rabbit hearts. It is therefore difficult to account for the protection we observed on the basis of an altered availability of energy[28,29] (ATP or creatine phosphate) and substrate (glycogen)[30] unless one argues that these substances were redistributed within the cell. In the case of ATP and creatine phosphate, there is evidence of functional[31] compartmentalization in heart muscle, and it is conceivable that long-term beta blockade is associated with a change in the size of the individual "pools," or their distribution or the extent and rapidity with which the ATP and creatine phosphate stored in them can be utilized.

Spieckermann et al.[29] described a close correlation between some of the deleterious effects of anoxia—including enzyme release—and the rate of depletion of the cardiac stores of ATP. However, because we found that the total stores of ATP, creatine phosphate and glycogen were unchanged by 5 to 6 days of treatment with propranolol, we cannot argue that the prolonged protective effect of propranolol treatment is due to an additional supply of energy-rich phosphates or glycogen substrate. The secondary effects of prolonged beta blockade in increasing action potential duration and in reducing sympathetic tone take 2 to 3 weeks to develop,[4,32] and it is therefore unclear whether the protective action of propranolol against the effect of hypoxia is related to these effects. There are other possibilities, including possible action of a metabolite or storage of some of the administered propranolol. Any storage system for propranolol must be one that during normal conditions of aerobic perfusion does not allow the drug access to the cardiac beta adrenoceptors; if it did, one would expect to find evidence of effective beta blockade. If propranolol is stored, it is theoretically possible that, like the catecholamines,[26] it is released in response to hypoxia.

Reduced availability of norepinephrine and protective effect on mitochondria: There are at least two possible explanations for our results, one involving a reduced availability of norepinephrine for release and the other associated with the failure of the mitochondria

from the hypoxic perfused hearts (Fig. 6) to accumulate Ca^{++} at a relatively rapid rate. Recently Raine and Chubb[32] reported reduced tyrosine hydroxylase and dopamine-beta-hydroxylase activities in cervical ganglia of rabbits pretreated for 6 days with a dose regimen of propranolol closely resembling that used in our study. They found that this effect of long-term beta blockade was evident on the 3rd day of treatment and had reached a high degree of significance by the 6th day. Because tyrosine hydroxylase is the rate-limiting enzyme in the biosynthesis of norepinephrine, it is possible that less endogenously stored norepinephrine is available for release in response to hypoxia in propranolol-treated than in control rabbit hearts. Such an effect could account for the prolonged protective effect of propranolol. This protection would be a secondary effect, due to a reduced amount of norepinephrine for release and not to the blockade of the beta adrenoceptors. The alternative explanation, involving the protection of the mitochondria against a phase of rapid Ca^{++}-accumulation, is equally plausible because it is well known[33] that Ca^{++}-accumulation interferes with mitochondrial function and ATP production. Our failure to detect any change in total tissue ATP does not argue against this possibility because of the probable complexity of the ATP storage "pools" in heart muscle. Further experiments are needed to differentiate between these two hypotheses.

Clinical implications: Our results show that a protective effect of propranolol on hypoxic heart muscle persists for up to 72 hours after cessation of therapy. This protection results in reduced rates of enzyme and myoglobin release and the preservation of mitochondrial function during periods of hypoxic substrate-free perfusion. The results support the concept[4,32] that there may be secondary consequences of prolonged beta adrenoreceptor blockade. If the results of these laboratory studies can be extrapolated to man, then it is possible that even when beta blockade has been terminated for several days (as, for example, before surgery) some protective effect of the therapy may persist, particularly with respect to the protection of the heart against the deleterious effects of an inadequate supply of oxygen. This protection may be due, in part at least, to either the reduced tyrosine hydroxylase activity described by Raine and Chubb[32] or a protective effect on mitochondria, particularly with respect to their Ca^{++}-accumulating activity.

References

1. **Nayler WG, Grau A, Yepez C:** β-adrenoceptor antagonists and the release of creatine phosphokinase from hypoxic heart muscle. Cardiovasc Res 11:344–352, 1977
2. **Nayler WG, Yepez CE, Fassold E:** Experimental studies on the effect of β-adrenoceptor antagonists on hypoxic heart muscle. In, Beta-Blockade in 1977 (Thieme G, ed). Stuttgart, Verlag Press, in press, 1978
3. **Nayler WG, Fassold E, Yepez C:** The pharmacological protection of mitochondrial function in hypoxic heart muscle: effect of verapamil, propranolol and methylprednisolone. Cardiovasc Res 12: 151–161, 1978
4. **Vaughan Williams EM, Raine AEG, Cabrera AA, et al:** The effects of prolonged β-adrenoceptor blockade on heart weight and cardiac intracellular potentials in rabbits. Cardiovasc Res 9:579–592, 1975
5. **Krebs HA, Henseleit K:** Untersuchungen über die Harnstoffbildung im Tierkörper. Hoppe-Seyler's Z Physiol Chem 210:33–66, 1932
6. **Langendorff O:** Untersuchungen am überlegenden Saugethierterzen. Pfluegers Arch 61:291–332, 1895
7. **Nayler WG, Seabra-Gomes R:** Effect of methylprednisolone sodium succinate on hypoxic heart muscle. Cardiovasc Res 10: 349–388, 1976
8. **Nayler WG, Grau A, Slade A:** A protective effect of verapamil on hypoxic heart muscle. Cardiovasc Res 10:650–662, 1976
9. **Oliver TA:** A spectrophotometric method for the determination of creatine phosphokinase and myokinase. Biochem J 61:116–122, 1955
10. **Sordahl LA, McCollum WB, Wood WG, et al:** Mitochondria and sarcoplasmic reticulum function in cardiac hypertrophy and failure. Am J Physiol 244:497–502, 1973
11. **Lindenmayer GE, Sordahl LA, Schwartz A:** Re-evaluation of oxidative phosphorylation in cardiac mitochondria from normal animals and in animals in heart failure. Circ Res 23:439–450, 1968
12. **Lowry OH, Rosebrough NJ, Farr AL, et al:** Protein measurement with the folin phenol reagent. J Biol Chem 193:265–275, 1951
13. **Scarpa A, Graziotti P:** Mechanisms of intracellular calcium regulation in the heart. 1. Stopped flow measurements of Ca^{2+} uptake by cardiac mitochondria. J Gen Physiol 62:756–772, 1973
14. **Hearse DJ, Humphrey SM:** Enzyme release during myocardial anoxia: a study of metabolic protection. J Mol Cell Cardiol 7: 463–482, 1975
15. **Sobel BE, Shell WE, Klein MS:** An isoenzyme of creatine phosphokinase associated with rabbit heart mitochondria. J Mol Cell Cardiol 4:367–380, 1972
16. **Opie LH, Mansford KRL, Owen P:** Effects of increased heart work on glycolysis and adenine nucleotides in the perfused heart of normal and diabetic rats. Biochem J 124:475–490, 1971
17. **Bergmeyer HU:** In, Methods of Enzymatic Analysis, Vol 3. New York, Verlag Chemie, Academic Press, 1974, p 1127–1131
18. **Lochner A, Kotze JCN, Gevers W:** Mitochondrial oxidative phosphorylation in myocardial anoxia: effects of albumin. J Mol Cell Cardiol 8:465–480, 1976
19. **Lochner A, Kotze JCN, Gevers W:** Mitochondrial oxidative phosphorylation in myocardial ischaemia: effects of glycerol, glucose and insulin on anoxic hearts perfused at low pressure. J Mol Cell Cardiol 8:575–587, 1976
20. **Sakai K, Spieckermann PG:** Effects of reserpine and propranolol on anoxia-induced enzyme release from the isolated perfused guinea-pig heart. Naunyn Schmiedebergs Arch Pharmacol 291: 123–130, 1975
21. **Reimer KA, Rasmussen M, Jennings RB:** Reduction by propranolol of myocardial necrosis following temporary coronary artery occlusion in dogs. Circ Res 33:353–363, 1973
22. **Maroko PR, Braunwald E:** Effects of metabolic and pharmacologic interventions on myocardial infarct size following coronary occlusion. Circ Res 53:Suppl I:I-162–I-168, 1976
23. **Winbury MW:** Influence of glucose on contractile activity of papillary muscle during anoxia. Am J Physiol 187:135–138, 1956
24. **Weissler AM, Kruger FA, Baba N, et al:** Role of anaerobic metabolism in the preservation of functional capacity and structure of anoxic myocardium. J Clin Invest 47:403–416, 1968
25. **Henry PD, Sobel BE, Braunwald E:** Protection of hypoxic guinea pig hearts with glucose and insulin. Am J Physiol 226:309–313, 1974
26. **Wollenberger A, Shahab J:** Anoxia-induced release of noradrenaline from the isolated perfused heart. Nature 207:88–89, 1965

27. **Maroko PR, Kjekshus JK, Sobel BE, et al:** Factors influencing infarct size following experimental coronary artery occlusions. Circulation 43:67–82, 1971
28. **McDonald TF, MacLeod DP:** Anoxia-recovery cycle in ventricular muscle: action potential duration, contractility and ATP content. Pfluegers Arch 325:305–322, 1971
29. **Spieckermann PG, Gebhard MM, Kalbow K, et al:** Freisetzung von Enzymen aus der Herzmuskelzelle während Saverstaffmangel. Verh Dtsch Ges Kreislauff Forsch 39:193–198, 1973
30. **Scheve RJ, Stezoski SW:** Protective role of increased myocardial glycogen stores in cardiac anoxia in the rat. Circ Res 27:835–849, 1970
31. **Gudbjarnason S, Mathes P, Ravens KG:** Functional compartmentation of ATP and creatine phosphate in heart muscle. J Mol Cell Cardiol 1:325–339, 1970
32. **Raine AEG, Chubb IW:** Long term β-adrenergic blockade reduces tyrosine hydroxylase and dopamine β-hydroxylase activities in sympathetic ganglia. Nature 267:265–267, 1977
33. **Chance B:** The energy-linked reaction of calcium with mitochondria. J Biol Chem 240:2729–2748, 1965

Beneficial Effects of Propranolol and Digitalis on Contraction And S-T Segment Elevation After Acute Coronary Occlusion

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Propranolol and digitalis each have limitations in acute myocardial infarction, the former because of negative inotropic effects and the latter because of increased ischemia. To evaluate their combined effects, ouabain (in a priming dose of 7.5 μg/kg body weight followed by 2 to 3 μg/kg per min intravenous infusion) and propranolol (1 mg/kg intravenously) were administered randomly in 22 open chest dogs after acute coronary occlusion, and changes were observed in epicardial S-T segment (10 to 14 sites) and local tension (strain gauge measurements). Heart rate was controlled by atrial pacing. After acute coronary occlusion, tension in the nonischemic zone decreased to 92.8 ± 3.4 percent of control level. Propranolol reduced it further to 67.3 ± 4.9 percent ($P < 0.005$), but ouabain increased it to 92.9 ± 4.9 percent ($P < 0.005$). Tension in the border zone decreased to 84.9 ± 4.11 percent ($P < 0.005$) after acute occlusion and to 54.5 ± 5.5 percent ($P < 0.001$) with propranolol but increased to 73.6 ± 5.1 percent ($P < 0.005$) with ouabain. Tension in the ischemic zone decreased from 59.3 ± 5.5 percent to 45.8 ± 5.0 percent ($P < 0.001$) with propranolol but was unaffected by ouabain. The sum of S-T elevation, which increased from 27.8 ± 5.3 to 72.1 ± 10.8 mv after occlusion, decreased to 62.8 ± 11.8 mv ($P < 0.05$) with propranolol and further to 53.0 ± 10.4 mv ($P < 0.005$) with ouabain. The pattern of changes in average S-T elevation was similar. When propranolol administration followed ouabain infusion, essentially similar effects on tension and the sum of S-T and average S-T elevation were observed. In summary, the combination of propranolol and digitalis favorably affects both tension and S-T segment abnormalities after acute coronary occlusion.

Both propranolol and digitalis have undergone considerable experimental and clinical study in acute coronary heart disease.[1–12] Experimentally, Libby[6] and Maroko[7] and their co-workers reported that propranolol decreases epicardial S-T segment elevation after coronary ligation and reduces myocardial creatine kinase (CK) depletion. More recently, Kloner et al.[13] indicated that propranolol also reduces microvascular injury in acute myocardial ischemia. However, concomitant with these effects, propranolol greatly decreases regional contraction,[14,15] an effect that significantly limits the feasibility of its use in acute myocardial infarction. On the other hand, digitalis significantly increases regional contraction after coronary ligation[11]; its effects on epicardial S-T segment abnormalities vary, depending on the presence or absence of a failing left ventricle.[7,16] In this study, we evaluated the combined effects on these regional functions of propranolol and digitalis in experimentally induced myocardial infarction.

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Methods

Experimental procedure: Experiments were performed in 22 mongrel dogs weighing 25 to 30 kg, anesthetized with sodium pentobarbital (30 mg/kg intravenously) and ventilated with a Harvard respirator. The heart was exposed through a mid sternal incision and supported in a pericardial cradle. A polyethylene tube was introduced through an external jugular vein for intravenous infusion. Central aortic and left ventricular pressures were monitored with fluid-filled stiff catheters introduced through the left femoral and right common carotid arteries, respectively, with use of Statham P23Db transducers. Fine (0.001 inch [0.00254 cm]) Teflon®-coated stainless steel wires were inserted in the right atrial appendage, and atrial pacing was achieved to control heart rate using a Medtronic battery-powered R wave coupled pulse generator (model 5837).

After the left anterior descending artery was isolated, 2 to 3 cm distal to its origin, the potentially ischemic and nonischemic zones were demarcated using epicardial electrograms and the areas were confirmed with use of methylene blue at the conclusion of each study as previously described.[17,18] Three Walton-Brodie strain gauge arches of 120 ohm resistance with adjustable feet were fixed with deep sutures in the potentially ischemic, border and nonischemic zones. The myocardial segment under the feet of each strain gauge was stretched by 30 percent of its initial length. The rate of rise in tension (dT/dt) was measured using a linear resistance-capacitance differentiating circuit from each zone.[17,18]

Epicardial electrograms were obtained with silver electrodes of 2 mm diameter mounted in acrylic plastic.[19] Ten to 12 electrodes were applied to the myocardial surface and kept in place with a silk thread running over the plastic bars and stabilized using the right and left sides of the pericardium. No epicardial sutures were used. This procedure permitted the electrodes to be kept in a fixed position throughout each experiment while pressure on the myocardium that could result in S-T segment changes was avoided. All epicardial recordings were obtained at a sensitivity level of 1 mm/mv and frequency limits of 0.1 to 100 hertz. Standard electrocardiographic lead II was also monitored throughout each experiment.

All records were taken on a multichannel oscilloscopic recorder (Electronics for Medicine) at paper speeds of 25 and 100 mm/sec. After control recordings were obtained, coronary occlusion was performed with a silk

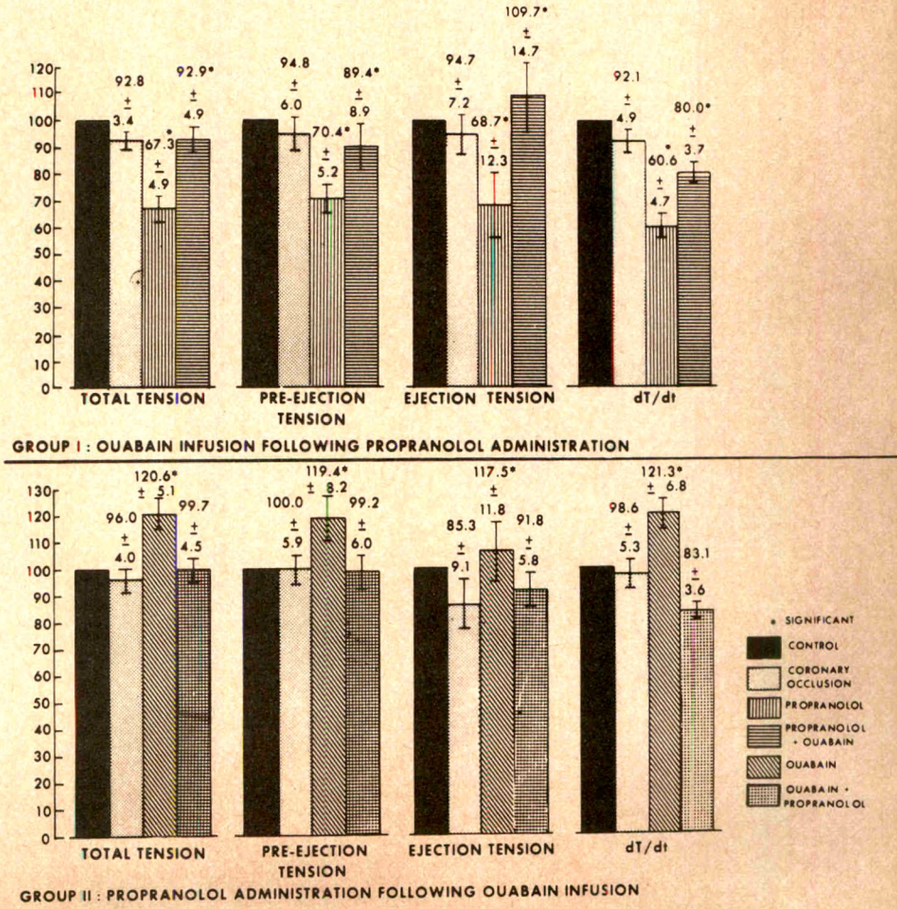

FIGURE 1. Effect of propranolol and ouabain on tension measurements in the nonischemic zone (see text).

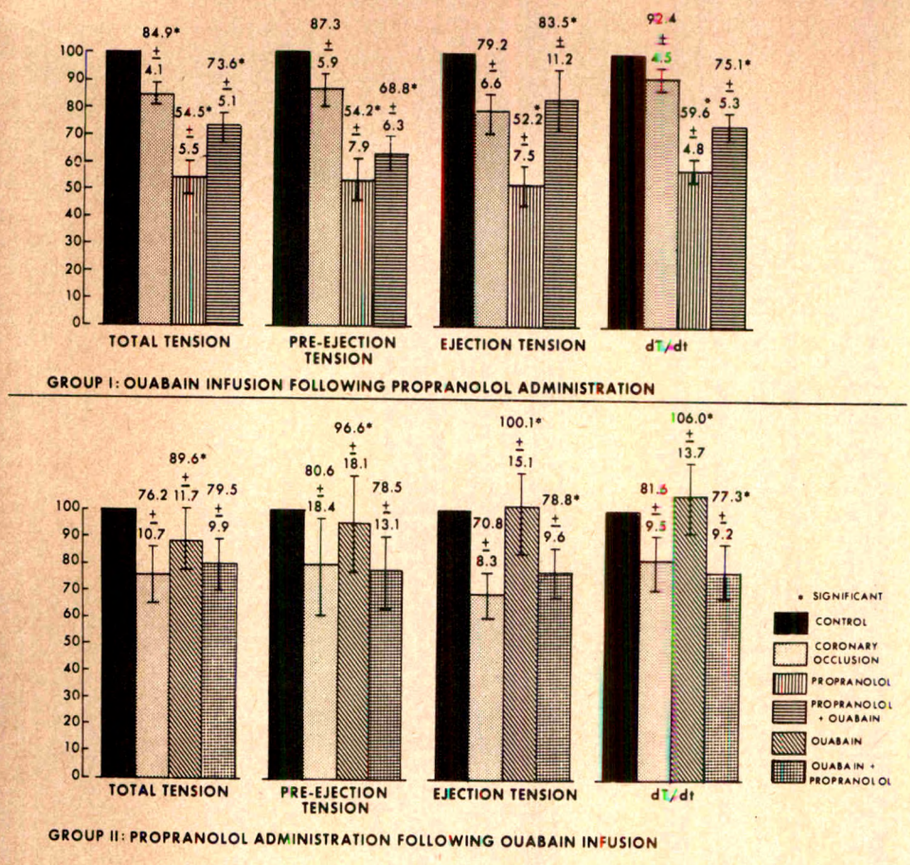

FIGURE 2. Effect of propranolol and ouabain on tension measurements in the border zone (see text).

ligature. A period of 10 minutes was permitted for stabilization of contractile changes, S-T segment and rhythm disturbances.

Tension measurements included preejection, ejection and total tension and rate of tension rise (dT/dt) expressed as percent of control.[18,19] S-T segment measurements were expressed as the sum of S-T segment elevation (ΣST) and average S-T elevation ($\overline{ST}$) in mv.[7,19] The paired *t* test was used for statistical analysis, and all observations were represented as mean ± standard error of the mean. Experiments were divided into two groups.

Group I (12 studies): After 30 minutes of coronary occlusion, propranolol (1 mg/kg body weight) was administered as an intravenous bolus injection. This dose is enough to produce beta receptor blockade and effectively blocks hemodynamic effects produced by 0.5 μg/kg of isoproterenol.[14,20] After 5 minutes of propranolol administration, ouabain infusion (priming dose of 7.5 μg/kg followed by 2 to 3 μg/kg per min) was instituted until toxicity developed, as indicated by the appearance of premature ventricular complexes or atrioventricular block. All recordings of tension and epicardial electrograms were made during atrial pacing at 1 minute intervals for 5 minutes after infusion of propranolol and at 5 minute intervals during infusion of ouabain.

Group II (10 studies): After 30 minutes of coronary occlusion, ouabain (7.5 μg/kg priming dose followed by 2 to 3 μg/kg per min) was infused initially until a 15 to 20 percent increase in tension in the nonischemic zone was observed; the infusion was followed by administration of propranolol (1 mg/kg). Recordings were obtained every minute (with controlled heart rates) until the maximal decrease in tension was observed.

Experiments showing significant changes in systemic blood pressure after coronary ligation or ischemic S-T segment elevation before coronary occlusion were excluded from analysis. At the end of each experiment, 2 cc of methylene blue dye was injected into the left anterior descending coronary artery immediately distal to the site of occlusion. With this technique we ascertained the area of the left ventricular myocardium this artery subserved and confirmed that gauges and epicardial electrodes were placed appropriately with respect to each zone.

Results

Effect on Tension Development

Nonischemic zone: *Group I:* Figure 1 (top panel) demonstrates the effects of propranolol and ouabain on tension measurements in Group I experiments, in which propranolol was administered first. Total tension in the nonischemic zone decreased to 92.8 ± 3.4 percent of

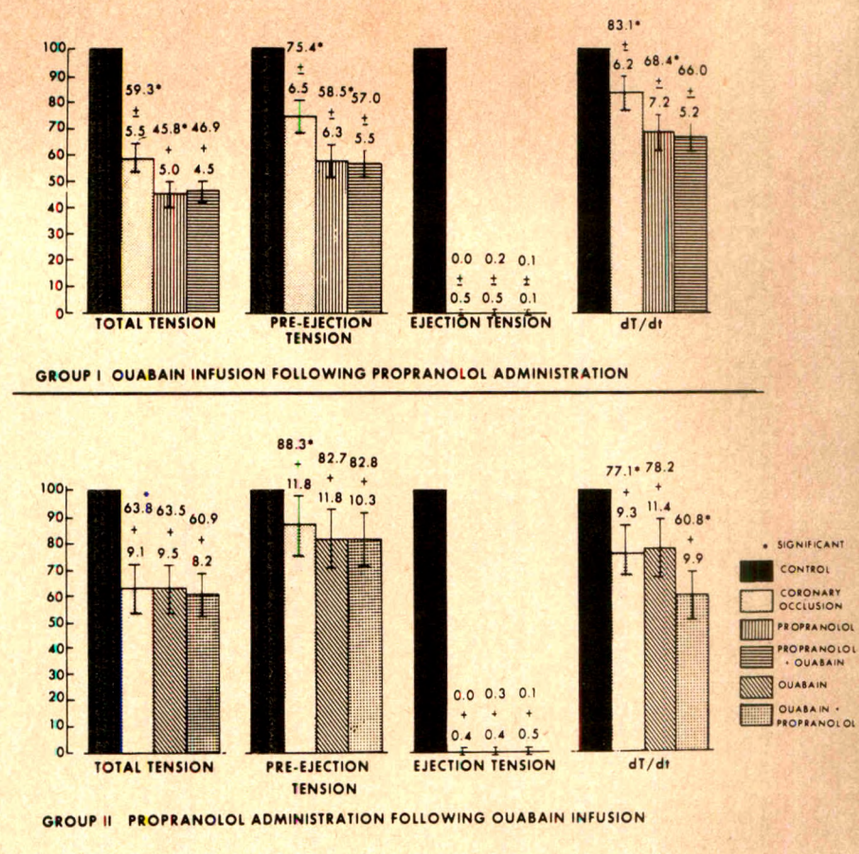

FIGURE 3. Effect of propranolol and ouabain on tension measurements in the ischemic zone (see text).

control level after coronary occlusion. After administration of propranolol, it decreased further to 67.3 ± 4.9 percent (P <0.005). Infusion of ouabain increased total tension significantly to 92.9 ± 4.9 percent (P <0.005).

Rate of tension rise (dT/dt) similarly decreased to 92.1 ± 4.9 percent of control level after coronary ligation and decreased further to 60.6 ± 4.7 percent (P <0.001) with administration of propranolol. Infusion of ouabain increased dT/dt to 80.0 ± 3.7 percent (P <0.005). The pattern of changes in preejection and ejection tension was similar to those of total tension and dT/dt. (Fig. 1).

Group II: In these experiments (Fig. 1, bottom panel), ouabain was administered first. Total tension, which had decreased to 96.0 ± 4.0 percent after coronary occlusion, increased significantly to 120.6 ± 5.1 percent (P <0.001) with ouabain. Administration of propranolol decreased total tension to 99.7 ± 4.5 percent (P <0.02) of control level. Changes in both preejection and ejection tension and dT/dt were directionally similar.

Border zone: *Group I:* The effects of propranolol and ouabain on local tension measurements of the border zone are represented in Figure 2. The border zone showed a significant decrease in total tension to 84.9 ± 4.11 percent of control level (P <0.005) after coronary ligation (Fig. 2, top panel). Administration of propranolol caused a further marked decrease in total tension to 54.5 ± 5.5 percent (P <0.001), which then increased to 73.6 ± 5.1 percent (P <0.005) with infusion of ouabain. dT/dt similarly decreased from 92.4 ± 4.5 percent of control level to 59.6 ± 4.8 percent (P <0.001) with propranolol and increased significantly to 75.1 ± 5.3 percent (P <0.001) with ouabain. Both preejection and ejection tension, which were severely depressed after coronary occlusion and administration of propranolol, showed similar improvement after infusion of ouabain (Fig. 2).

Group II: In these experiments (Fig. 2, bottom panel) total tension, which had decreased to 76.2 ± 10.7 percent of control level after coronary occlusion, increased to 89.6 ± 11.7 percent (P <0.001) with ouabain. After the subsequent administration of propranolol, total tension decreased to only 79.5 ± 9.9 percent of control value (difference not significant). dT/dt similarly increased from 81.6 ± 9.5 percent of control level to 106 ± 13.7 percent (P <0.02) after infusion of ouabain and decreased only to 77.37 ± 9.2 percent (P <0.005) with propranolol. Changes in preejection tension were similar in direction. Ejection tension, which showed a marked decrease to 70.8 ± 8.3 percent (P <0.02) after coronary occlusion, increased to 100.1 ± 15.1 percent (P <0.05) with ouabain and then decreased to 78.8 ± 9.6 percent with propranolol (P <0.05).

Ischemic zone: *Group I:* Total tension in the ischemic zone decreased to 59.3 ± 5.5 percent (P <0.001) of control level after coronary ligation and decreased further to 45.8 ± 5.0 percent (P <0.001) with propranolol (Fig. 3, top panel). Infusion of ouabain produced no

further change (46.9 ± 4.5 percent). Preejection tension and dT/dt changed similarly. Ejection tension which had decreased to 0.0 ± 0.5 percent of control level after coronary occlusion, was unchanged by propranolol or ouabain.

Group II: Neither infusion of ouabain nor infusion of propranolol resulted in a significant change in the ischemic zone (Fig. 3, bottom panel). The total tension was 63.8 ± 9.1 percent of control level after coronary occlusion, 63.5 ± 9.5 percent after ouabain and 60.9 ± 8.2 percent after propranolol infusion. Preejection and ejection tension and dT/dt showed similar responses. Figures 4 and 5 show a typical experiment demonstrating the effects of infusion of propranolol and ouabain on local tension in Group I and Group II, respectively.

Effect on S-T Segment

The effects of infusion of propranolol and ouabain on epicardial S-T segment elevations are shown in Figure 6.

Group I: The sum of S-T elevation (ΣS-T) increased from 27.8 ± 5.3 to 72.1 ± 10.8 mv (P <0.001) after coronary occlusion. Administration of propranolol decreased this value to 62.8 ± 11.8 mv (P <0.05). With infusion of ouabain, ΣST decreased further to 53.0 ± 10.4 mv (P <0.005) (Fig. 6, top panel). The pattern of changes in average S-T elevation ($\overline{ST}$) was similar.

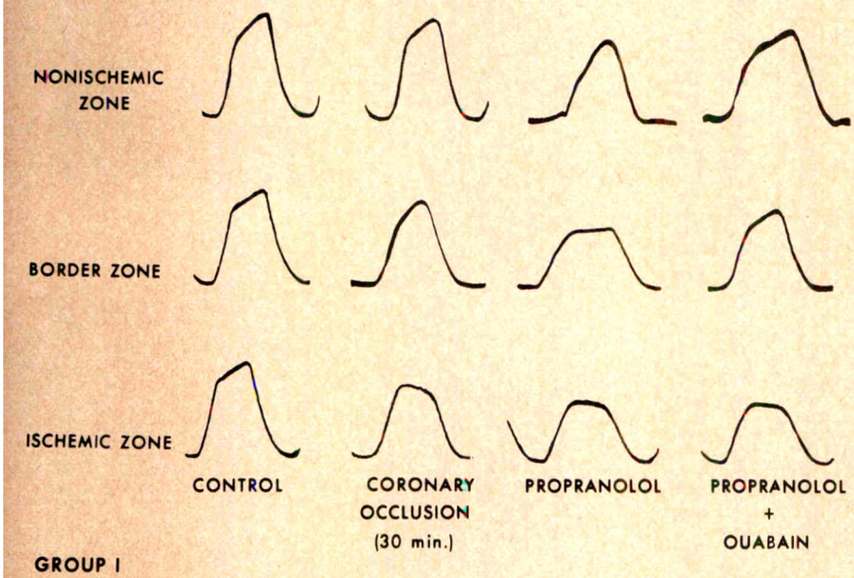

FIGURE 4. A typical Group I experiment demonstrating the effect of propranolol and ouabain on local tension in the nonischemic, border and central ischemic zones after coronary occlusion. After administration of propranolol, there is a significant reduction in total tension in all three zones. After infusion of ouabain, both the nonischemic and border zones show marked improvement in tension; the ischemic zone remains unchanged.

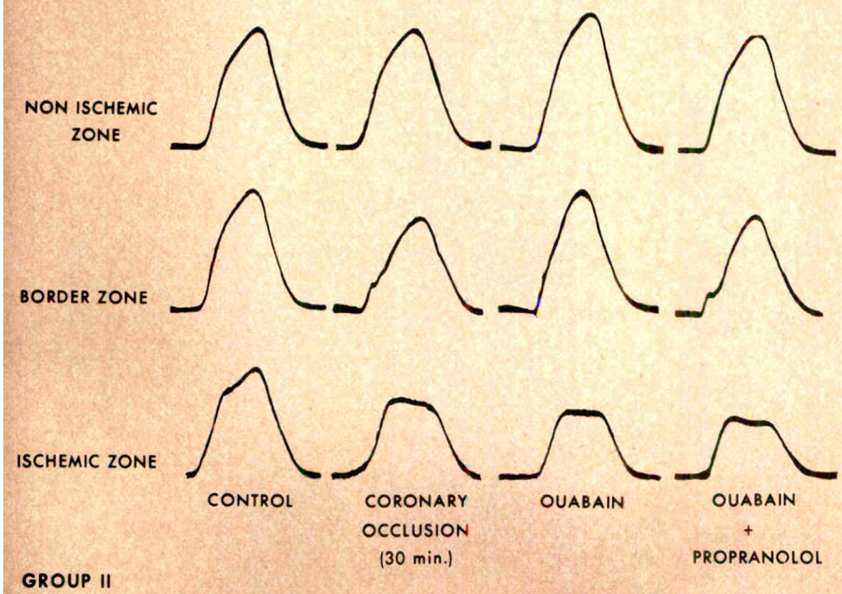

FIGURE 5. Typical Group II experiment demonstrating the effect of propranolol and ouabain on local tension in the nonischemic, border and central ischemic zones after coronary occlusion. After infusion of ouabain, there is a significant increase in tension in both the nonischemic and border zones; ischemic zone tension is unchanged. With administration of propranolol, tension in the border and nonischemic zones decreases only to control postcoronary occlusion levels. The decrease in tension after administration of propranolol is significantly less than that in the Group I experiments (see Results).

Group II: The sum of S-T elevation (ΣST) increased from 21.8 ± 3.2 to 68.5 ± 12.3 mv (P <0.005) after coronary occlusion. Infusion of ouabain decreased ΣST insignificantly to 65.3 ± 11.1 mv. However, propranolol resulted in a further decrease to 53.3 ± 10.0 mv (Fig. 6, bottom panel). The pattern of changes in average S-T elevation ($\overline{ST}$) was similar. Figure 7 represents a typical experiment demonstrating the effect of infusional propranolol and ouabain on S-T segment elevation in epicardial electrograms.

Effect on Heart Rate, Blood Pressure and Left Ventricular End-Diastolic Pressure

Propranolol administration caused a significant reduction of heart rate from 171.4 ± 5.1 to 119.6 ± 5.7 beats/min (P <0.001), but the addition of ouabain

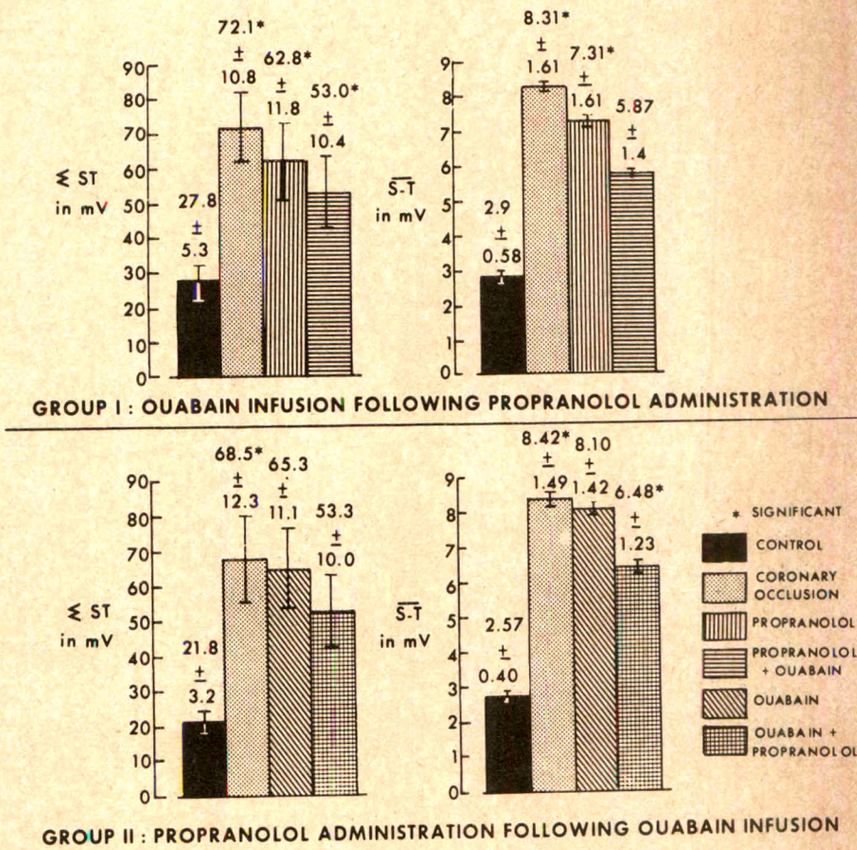

FIGURE 6. Effect of propranolol and ouabain on epicardial S-T segment elevation. ΣST = sum of ST elevation; $\overline{ST}$ = average S-T elevation; bars indicate standard error of the mean.

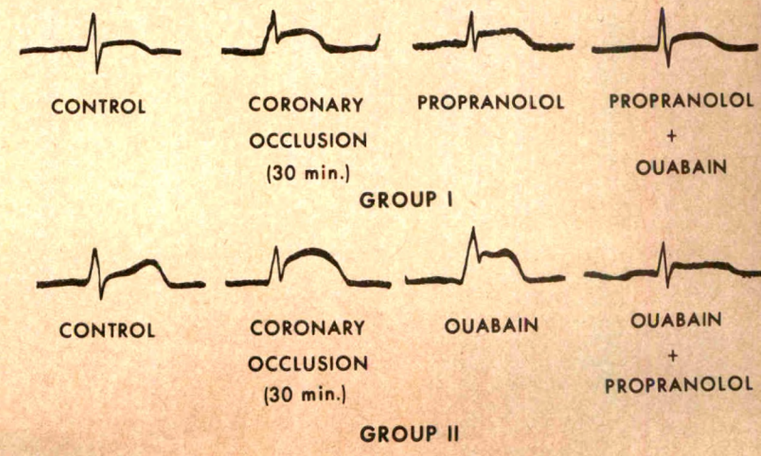

FIGURE 7. Typical Group I and Group II experiments demonstrating the effect of propranolol and ouabain on epicardial S-T segments. In the Group I experiment, administration of propranolol decreases S-T segment elevation. Infusion of ouabain causes a further decrease in S-T elevation. In the Group II experiment, initial infusion of ouabain does not change the S-T elevation significantly; administration of propranolol causes a significant decrease in S-T elevation.

caused no further change (123.1 ± 4.3 beats/min). Neither drug significantly changed systolic or diastolic blood pressure. Left ventricular end-diastolic pressure increased insignificantly from 13.5 ± 1.7 to 16.0 ± 0.87 mm Hg with propranolol administration and decreased minimally to 15.1 ± 1.0 mm Hg with infusion of ouabain.

Discussion

Considerable interest has focused on quantifying and modifying the size of an acute myocardial infarction, and propranolol has been considered a "prototype" agent in this regard.[21] Although several studies have indicated that propranolol decreases the magnitude of epicardial S-T segment abnormalities after acute coronary ligation,[6,7,14] this decrease is accompanied by a concomitant decrease in regional contraction.[14] Nonetheless, propranolol has been reported[1] to be efficacious in at least some patients with acute myocardial infarction. The clinical usefulness of digitalis in acute myocardial infarction is somewhat unclear,[8–10,22,23] and the effects of this agent on epicardial S-T segment abnormalities in experimental studies have been variable, depending on the status of the left ventricle. Digitalis therefore differs from other inotropic agents in this setting,[7,16] although it does increase regional contraction in the nonischemic and border zones after acute coronary ligation.[11]

Effects of combined propranolol and digitalis therapy: In the clinical setting of chronic heart disease, propranolol has also been shown to induce or accentuate regional contraction abnormalities,[24] whereas digitalis has been demonstrated to be efficacious with respect to regional contraction.[25] In addition, several studies using both invasive and noninvasive methods[26–29] have shown that the combination of propranolol and digitalis is useful in patients with abnormal left ventricular performance and that digitalis is effective in cardiac failure induced by beta receptor blockade.[26] In patients with angina pectoris administration of digitalis does not interfere with the antianginal effect of propranolol, thus suggesting that the glycoside does not adversely affect the beta blockade in reducing myocardial oxygen requirements.

The results of our experimental study in the setting of acute coronary ligation also suggest the utility of this combination. In the nonischemic zone, tension measurements all decreased significantly after administration of propranolol, and this effect was readily reversed to near prepropranolol levels by ouabain administration (Fig. 1). In the border zone, all tension measurements also decreased significantly after coronary ligation and decreased further after administration of propranolol (Fig. 2). However, ouabain infusion then increased tension development, to levels close to those observed after coronary occlusion. Observations were similar regardless of which agent was administered initially. There was no statistically significant difference in tension development with the combination of propranolol and ouabain in Group I and Group II experiments. Central ischemic zone tension was unaffected by either agent alone or in combination. These observations are consistent with preliminary data reported by Vatner et al.[30]

Concomitant with these contractile effects, ouabain further diminished the epicardial S-T segment abnormalities, which decreased significantly after administration of propranolol (Fig. 6 and 7). Ouabain infused as the initial agent had no significant effects on S-T segment abnormalities, but subsequent administration of propranolol significantly decreased these abnormalities.

Clinical implications: There are many difficulties in extrapolating this type of experimental data to the clinical setting. In addition, caution must be exercised concerning the interpretation of S-T segment changes as the sole indicator of ischemia.[19,32,33] Clinically, propranolol has been found efficacious in the treatment of at least some patients with acute myocardial infarction.[1] To the degree that our experimental data can be extrapolated to man, they support the utility of adding digitalis to the regimen when propranolol therapy is considered advisable in patients with acute coronary heart disease. They also suggest that digitalis may be efficacious in propranolol-treated patients with acute coronary heart disease who subsequently exhibit impending or overt left ventricular failure.

References

1. **Mueller HS, Ayres SM, Religa A, et al:** Propranolol in the treatment of acute myocardial infarction. Effect on myocardial oxygenation and hemodynamics. Circulation 49:1078–1087, 1974
2. **Pelides LJ, Reid DS, Thomas M, et al:** Inhibition by β-blockade of the ST segment elevation after acute myocardial infarction in man. Cardiovasc Res 6:295–301, 1972
3. **Balcon R, Jewitt DE, Davies JPH, et al:** A controlled trial of propranolol in acute myocardial infarction. Lancet 2:917–920, 1966
4. A multicenter trial: propranolol in acute myocardial infarction. Lancet 2:1435–1438, 1966
5. **Gold HK, Leinbach RC, Maroko PR:** Reduction of myocardial injury in patients with acute infarction by propranolol (abstr). Circulation 49, 50: Suppl II:II-33, 1974
6. **Libby P, Maroko PR, Covell JW, et al:** Effect of practolol on the extent of myocardial ischemic injury after experimental coronary occlusion and its effects on ventricular function in the normal and ischemic heart. Cardiovasc Res 7:167–173, 1973
7. **Maroko PR, Kjekshus JK, Sobel BE, et al:** Factors influencing infarct size following experimental coronary artery occlusions. Circulation 48:67–81, 1971
8. **Rahimtoola SH, DiGilio MM, Sinno Z, et al:** Effects of ouabain on impaired left ventricular function during convalescence after acute myocardial infarction. Circulation 44:866–876, 1971
9. **Rahimtoola SH, Sinno MZ, Chuquimia R, et al:** Effects of ouabain on impaired left ventricular function in acute myocardial infarction. N Engl J Med 287:527–531, 1972
10. **Hodges M, Mriesing GC, Riggins RCK, et al:** Effects of intravenously administered digoxin on mild left ventricular failure in acute myocardial infarction in man. Am J Cardiol 29:749–756, 1972

11. **Banka VS, Chadda KD, Bodenheimer MM, et al:** Digitalis in experimental acute myocardial infarction. Differential effects on contractile performance of ischemic, border and nonischemic ventricular zones in the dog. Am J Cardiol 35:801–808, 1975
12. **Dodek A:** Digitalis use in acute myocardial infarction: current concepts. Can Med Assoc J 111:561–564, 1974
13. **Kloner RA, Fishbein MC, Cotran RS, et al:** The effect of propranolol on microvascular injury in acute myocardial ischemia. Circulation 55:872–880, 1977
14. **Bodenheimer MM, Banka VS, Helfant RH:** Propranolol in experimental myocardial ischemia: dissociation of effects on contraction and epicardial ST segments. Am Heart J 92:481–486, 1976
15. **Liang C, Hood WB:** The myocardial depressant effect of beta-receptor blocking agents: comparative study of dl-propranolol, d-propranolol and practolol in awake dogs with and without acute myocardial infarction. Circ Res 35:272–280, 1974
16. **Watanabe T, Covell JW, Maroko PR, et al:** Effects of increased arterial pressure and positive inotropic agents on the severity of myocardial ischemia in the acutely depressed heart. Am J Cardiol 30:371–377, 1972
17. **Banka VS, Helfant RH:** Temporal sequence of dynamic contractile characteristics of ischemic and nonischemic myocardium following acute coronary ligation. Am J Cardiol 34:158–163, 1974
18. **Banka VS, Chadda KD, Helfant RH:** Limitations of myocardial revascularization in restoration of regional contraction abnormalities produced by coronary occlusion. Am J Cardiol 34:164–170, 1974
19. **Bodenheimer MM, Banka VS, Levites R,** Temporal relation of epicardial electrographic, contractile and biochemical changes after acute coronary occlusion and reperfusion. Am J Cardiol 37:486–492, 1976
20. **Nakano J, Kusakari T:** Effect of beta adrenergic blockade on the cardiovascular dynamics. Am J Physiol 210:833–837, 1966
21. **Jennings RB, Reimer KA:** Salvage of ischemic myocardium. Mod Concepts Cardiovasc Dis 43:125–130, 1974
22. **Balcon R, Hoy J, Sowton E:** Hemodynamic effects of rapid digitalization following acute myocardial infarction. Br Heart J 30: 373–376, 1968
23. **Malmcrona R, Schroder G, Werko L:** Hemodynamic effects of digitalis in acute myocardial infarction. Acta Med Scand 18:55–63, 1966
24. **Helfant RH, Herman MV, Gorlin R:** Abnormalities of left ventricular contraction induced by beta adrenergic blockade. Circulation 43:641–647, 1971
25. **O'Rourke RA, Henning H, Theroux P, et al:** Favorable effects of orally administered digoxin on left heart size and ventricular wall motion in patients with previous myocardial infarction. Am J Cardiol 37:708–715, 1976
26. **Crawford MH, LeWinter MM, O'Rourke RA, et al:** Combined propranolol and digoxin therapy in angina pectoris. Ann Intern Med 83:449–455, 1975
27. **Ekelung LG, Johnsson G, Melcher A, et al:** Effects of cedilanid-D and alprenolol in angina pectoris. Eur J Clin Pharmacol 6:113–118, 1973
28. **Gebhardt W, Blumchen G:** Hemodynamic effects of a combined therapy with propranolol and digoxin. Cardiologia 52:190–195, 1968
29. **Bachour G, Bender F, Hochrein H:** Hamodynamische Reaktionen nach Prindolol and Digitalis bei akutem Herzinfarkt. Med Klin 71: 414–420, 1976
30. **Vatner SF, Murray PA, Baig H:** Salutary action of a cardiac glycoside combined with propranolol in the ischemic heart of the conscious dog (abstr). Clin Res 25:457A, 1977
31. **Helfant RH, Banka VS, Bodenheimer MM:** Perplexities and complexities concerning the myocardial infarction border zone and its salvage. Am J Cardiol 41:345–347, 1978
32. **Holland RP, Brooks H:** TQ-ST segment mapping: Critical review and analysis of current concepts. Am J Cardiol 40:110–129, 1977
33. **Surawicz B:** The disputed S-T segment mapping: is the technique ready for wide application in practice? Am J Cardiol 40:137–140, 1977

Regional Redistribution of Myocardial Blood Flow After Coronary Occlusion and Reperfusion in the Conscious Dog

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Early and late changes in regional myocardial blood flow distribution within the left circumflex coronary arterial bed after occlusion and after occlusion and reperfusion were compared with the extent of myocardial tissue necrosis. Radiolabeled microspheres, 15 μm, were used to study regional myocardial blood flow in conscious dogs at 5 minutes, 2 and 6 hours and 1 month after coronary occlusion. Blood flow was measured in conscious dogs whose hearts were reperfused for 72 hours after 2, 6 and 24 hours of occlusion. Blood flow was measured in four distinct transmural myocardial zones delineated by dye injections and gross infarct features of the occluded left circumflex coronary bed. After occlusion, myocardial flow was redistributed from deep layers to outer layers, and within 6 hours after occlusion collateral flow was increased to the outer zones in excess of redistributed flow. After reperfusion, blood flow greatly increased to regions containing predominantly normal tissue, and flow was redistributed away from the necrotic zones. The indigenous collateral circulation was a major determinant of infarct size in the occluded and reperfused myocardium. The concept of a migrating and narrowing marginal zone is discussed.

Ultimately, salvaging ischemic myocardium depends on the stage of development of the coronary collateral circulation at the onset of ischemia and on the rapidity with which blood flow to the ischemic region can be increased. Previous investigators[1–4] have reported the extent of myocardial blood flow in the ischemic, marginal and nonischemic zones after acute coronary occlusion in experimental animals. At least one study[2] has also established a quantitative relation between myocardial blood flow after coronary occlusion and the extent of subsequent infarction. Studies in experimental myocardial infarction[5,6] have shown that the ultimate size of an infarct can be reduced by restoring blood flow (instituting reperfusion) in the early phase of ischemia. What effect the inherently developed coronary collateral circulation has on reperfusion or on evolving changes in blood flow in the ischemic zone has not been shown. We undertook this study (1) to determine sequential changes in myocardial blood flow to ischemic regions after specific intervals of coronary occlusion and reperfusion, and (2) to assess how coronary collateral development and reperfusion affect the relation of myocardial blood flow to the extent of subsequent myocardial infarction.

Methods

Animal Preparation

To avoid introducing variables with anesthesia, we performed our studies in conscious animals. We used 120 chronically instrumented mongrel dogs of either sex weighing 23 ± 0.1 kg (mean ± standard error of the mean). We have described our animal preparation in detail elsewhere.[3,7] Briefly, during left thoractomy Biotronex electromagnetic flow probes were placed on the root of the aorta and on the left circumflex coronary artery just distal to its origin. An inflatable cuff

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TABLE I
Experimental Groups

	Occlusion Only			Occlusion and Reperfusion				
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8
Length of occlusion	4 days	4 days	1 month	2 hr	6 hr	6 hr	24 hr	6 hr
Duration of reperfusion	None	None	None	72 hr	72 hr	72 hr	72 hr	1 month
Measured* distribution of flow	5 min AO 2 hr AO 6 hr AO	5 min AO 2 hr AO 6 hr AO	Before O 5 min AO 1 mo AO	5 min AO 1 hr AR 72 hr AR	5 min AO 1 hr AR 72 hr AR	5 min AO 1 hr AR 72 hr AR	5 min AO 1 hr AR 72 hr AR	Control 1 hr AR 1 mo AR
Interval between implantation & occlusion	36 hr	3 wk	3 wk	3 wk	36 hr	3 wk	3 wk	3 wk
Survival (no.)	6 of 7	6 of 6	6 of 6	5 of 7	5 of 7	5 of 8	5 of 7	4 of 5

* Measured with radiolabeled microspheres.
AO = after occlusion; AR = after start of reperfusion; O = occlusion.

was also placed on the left circumflex coronary artery just distal to the probe. Silastic® catheters were placed in the left atrium and the aorta. The dogs recovered in large open laboratory runs permitting spontaneous exercise and were trained to lie quietly on a padded table for several hours while fully conscious. The laboratory was kept quiet to obtain low resting heart rates. Flows were monitored with a Biotronex BL-310 flowmeter, and pressures were measured with Elema-Schönander transducers. Phasic pressure and flow signals and lead II of an electrocardiogram were recorded on an Elema-Schönander Mingograf 81 ink-jet recorder. The phasic recordings were subjected to planimetry, and pressures and flows were calculated.

Experimental Design

The animals were separated into eight experimental groups (Table I). In Groups 1 to 3 (control groups), the left circumflex coronary artery was permanently occluded at two different intervals after instrument implantation. In Groups 4 to 8, the left circumflex coronary artery was occluded for a certain interval and then allowed to reperfuse itself after set periods. Flow distribution was determined at standardized intervals after occlusion and the institution of reperfusion. In both the control and reperfusion groups, occlusion was begun at different intervals after instrument implantation to permit or avoid increasing collateralization before the occlusion. For example, Groups 5 and 6 were identical except for differences in the interval between implantation and occlusion (Table I). The survival rate in Table I reflects the number of animals that manifested fibrillation at some point in the project and thus were excluded from the study; for example, one dog was excluded from Group 1.

All dogs were given procainamide (200 mg intravenously and 200 mg intramuscularly) 15 minutes before measurements in the control, occlusion and reperfusion periods. To avoid the possibility of increased hemorrhage into the infarcts, heparin was not administered. Hemodynamic variables, including aortic flow, aortic pressure and left circumflex coronary arterial flow, and lead II of an electrocardiogram were measured before occlusion and 5 minutes and 2, 6, 24 and 72 hours after occlusion, and before and after release of the occlusion that began reperfusion.

Microsphere Method

Radiolabeled microspheres were used to measure the distribution of blood flow throughout the myocardium. Our methods have been described in detail elsewhere.[3] Briefly, we obtained polystyrene microspheres, 15 μm in diameter and labeled with cerium-143, chromium-51 or strontium-85 (3M Company, St. Paul, Minnesota). These were suspended in a 10 percent solution of dextran. After the radioactivity per volume of these microspheres was established, the microspheres were vigorously mixed, and measured volumes were injected into the animal circulation through the left atrial catheter. Table I shows the points at which these injections were made to measure blood flow distribution. Hemodynamic variables were also measured at these points.

The tissue was analyzed for the distribution of the microspheres on a Packard Auto-gamma spectrometer, model 5912, equipped with a multichannel analyzer. The spectrometer measured the energy emitted in the photo peak window of each isotope. From these measurements the radioactivity per gram of tissue was calculated according to the methods of Rudolph and Heymann[8] using a Hewlett-Packard 9825A programmable calculator. The heart was prepared for gamma spectrometry as described under Postmortem Studies.

Experiments to determine optimal microsphere procedures: Because recent reports[9,10] have suggested that microspheres may be lost from ischemic myocardium after 24 hours of occlusion, we separated an additional 64 animals into four groups (A to D) to determine the effects of sample size, number of microspheres injected and the order of microspheres injected on the optimal number of microspheres in ischemic myocardial samples and the degree of loss of microspheres from ischemic myocardium. These four groups were as follows:

Group A: 22 conscious dogs injected with strontium, chromium or cerium-labeled microspheres selected in a round robin manner; these animals served as controls (no occlusion). After 3 days the dogs were killed, and 4 g samples were taken from the endocardial and epicardial regions of both the left circumflex and the left anterior descending arterial beds. The samples were air-dried and packed into a single counting tube.

Group B: 21 dogs injected with strontium- and chromium-labeled microspheres before and after occlusion of the left circumflex coronary artery. The animals were killed 2 to 4 days after occlusion, and 4 g samples were taken from the endocardial and epicardial regions of the left anterior descending arterial bed and 1 g samples from the ischemic left circumflex bed.

Group C: 11 conscious dogs injected first with strontium-labeled microspheres before occlusion of the left circumflex coronary artery and then with chromium- and cerium-labeled

TABLE II
Microsphere Loss From Ischemic Myocardium (mean ± standard error of the mean)

Group*	no. of Dogs	Microspheres Injected (no.) ($\times 10^6$)	Tissue Sample Size (g)	Flow Ratios† LCC/LAD Endo	Flow Ratios† LCC/LAD Epi
A (control)	22	2	4	0.98 ± 0.03	1.06 ± 0.02‡
B (occlusion 2–4 days)	21	2	1	0.90 ± 0.03§	0.99 ± 0.02‖
C (occlusion 2–4 days)	11	2	4	0.94 ± 0.03	0.99 ± 0.03
D (occlusion 2–4 days)	10	6	1	0.97 ± 0.03	0.99 ± 0.03
3 (occlusion 1 month)	6	6	0.5–1.5	0.48 ± 0.09§	0.90 ± 0.16‖
8 (occlusion + reperfusion (1 month)	4	6	0.5–1.5	0.56 ± 0.10§	0.91 ± 0.11‖

* Dogs in control group A were killed 3 days after microsphere injection. Data on Groups B, C, D, 3 and 8 are provided under Methods.

† Microsphere flow ratios for endocardial (ENDO) and epicardial (EPI) zones of the left circumflex (LCC) and left anterior descending (LAD) coronary arterial beds. Significance of differences at a probability (P) level of <0.05; ‡ = epicardial control value compared with endocardial control value; § = endocardial value compared with endocardial control value; ‖ = epicardial value compared with epicardial control value.

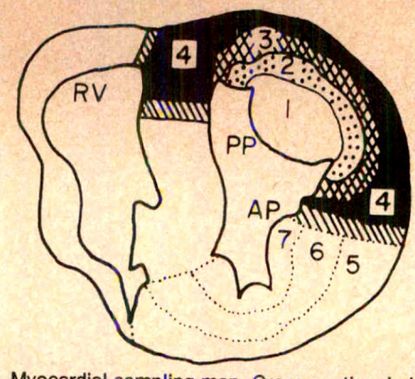

FIGURE 1. Myocardial sampling map. Cross-sectional view of myocardium showing division into zones of study. 1 = central necrotic core; 2 = ischemic zone; 3 = marginal zone; 4 = jeopardized zone. Diagonal striped areas are the discarded margins. 5, 6 and 7 = epicardial, mid wall and endocardial regions, respectively. AP = anterior papillary muscle; PP = posterior papillary muscle; RV = right ventricle.

microspheres after occlusion. The dogs were killed 2 to 4 days after occlusion, and 4 g samples were selected from the ischemic left circumflex bed and from endocardial and epicardial regions of the left anterior descending arterial bed. In Groups A to C, 2×10^6 tracer microspheres were injected each time.

Group D: 10 conscious dogs injected with 6×10^6 tracer microspheres as follows: strontium-labeled microspheres before coronary occlusion and chromium- and cerium-labeled microspheres after occlusion. The animals were killed 2 to 4 days after occlusion, and 4 g samples were taken from both endocardial and epicardial regions of the left anterior descending arterial bed and four 1 g samples from the ischemic left circumflex bed. Each 1 g sample was counted, calculated separately and then averaged with the others. The data from Groups A to D and experimental Groups 3 and 8 are presented in Table II.

The energy spectra of gamma emitters range from high to low in the following order: strontium, chromium, cerium. This order was used in the experimental Groups 1 to 8 to optimize minimal spectral overlap under conditions where the number of microspheres is low.[8]

Calculation of blood flows: Blood flows for the various regions of the myocardium were calculated using the aortic flow measured with the aortic flow probe. These flows were expressed as regional myocardial blood flow in ml/min per 100 g using the formula:

$$\text{RMBF} = \text{cpm/g T/cpm I} \times \text{AF} \times 100,$$

where cpm/g T is the counts per minute per gram of tissue, cpm I is the counts per minute injected and AF is aortic flow (ml/min).

Flow to the left circumflex coronary arterial bed was measured with the flow probe. This probe was used to verify complete occlusion of the coronary artery and to ensure that no reperfusion was allowed prematurely. It also allowed measurement of reactive hyperemia after reperfusion. It has been shown[6] that reactive hyperemia may occur on reperfusion. In this study, flow that was not the result of reactive hyperemia was measured using injection of microspheres 1 hour after reperfusion. This hour allowed the immediate response of reactive hyperemia to dissipate.

Postmortem Studies

Post mortem, the coronary arteries were injected with dyes at a perfusion pressure of 100 mg Hg to distinguish the vascular beds. The heart was examined grossly and microscopically for necrosis, and the tissue was mapped and analyzed in a gamma spectrometer to measure the distribution of the microspheres in the circulation.

The dogs in Groups 3 and 8 were studied 1 month after the onset of occlusion; all other animals were killed 4 days after the onset of occlusion (Table I). Thus, the myocardial infarct zone was easily identified grossly. The left circumflex coronary artery was examined grossly for patency in the reperfusion groups and for complete occlusion in the groups with permanent occlusion. We found that the cross-sectional area of the artery immediately under the flow probe ranged from 50 to 90 percent of the area of the normal left circumflex coronary artery proximal to the probe. This stenosis should have induced collateral development.[11] After the heart was excised, the left circumflex and left anterior descending coronary arteries were cannulated. In the dogs with arterial occlusion it was necessary to cannulate distal to the occlusive cuff. To define the margin between the anatomic distribution of these vascular beds, Trypan blue dye was injected into the anterior descending artery, and acridine orange was injected into the circumflex artery simultaneously.

Infarct zones: The hearts were sliced transversly, the vascular beds identified and the infarct zones mapped (see Histologic Methods). Both the circumflex and the left anterior descending arterial beds were divided transmurally into four transmural layers. The left anterior descending coronary bed was divided into four equal layers; the circumflex bed was divided transmurally according to necrotic landmarks. These zones were subdivided into samples of 1 to 3 g and placed in couting vials with formalin. The border between two adjacent beds (shown in Fig. 1 as the zone with diagonal stripes) was approximately 8 mm thick and separated the left circumflex

coronary arterial bed from the other two vascular beds. This zone was discarded to avoid tissue samples with interdigitating blood supply from the two arteries.

The following experiment was performed to determine if interdigitating flow from the unoccluded artery might influence the flow measurements. The method of separating the beds was tested in three dogs placed on a left circumflex coronary arterial bypass as previously described.[1] Radioactive microspheres were injected into the left atrium of these open chest dogs while the left circumflex coronary artery was separately perfused with microsphere-free blood at normal perfusion pressure. The heart was excised, and the left circumflex coronary arterial bed was identified using the dye injection method described. The left circumflex coronary arterial bed, less the 8 mm border, was divided into four transmural sections. These sections were from what would be infarct tissue in the experimental groups. Flow from the other arteries to the outer section of the left circumflex coronary arterial bed, analogous to the jeopardized zone in the experimental groups, averaged 4 ± 1 ml/min per 100 g. Once the 8 mm margins were removed, the total of such flow to the other three sections from the other two arteries was sufficiently low (about 1 ml/min per 100 g) to justify ignoring it in the experimental groups.

Histologic Studies

The transverse sections of the hearts of both the occlusion and reperfusion groups were examined grossly, and the various zones of the left circumflex coronary arterial bed were identified by the following features (Fig. 1): The necrotic core was a pale grey zone in the endocardium. The ischemic zone was brown and hemorrhagic. Outside the ischemic zone was a grey-brown zone of granulation tissue designated marginal. The so-called border zone of interdigitating flow[12] between the two adjacent beds was not studied in these experiments. It was discarded in the 8 mm border tissue. Our marginal zone is the zone of intermediate flow seen transmurally in the bed at risk. The normal-appearing tissue immediately outside the marginal zone was designated the jeopardized zone. In the reperfusion groups, hemorrhagic areas were more extensive than in occlusion groups and were included in the ischemic zone.

The weight of each piece of tissue from each zone was determined at the time of necropsy. These weights were summed to determine zone size in grams. Zone size as percent of infarct was determined by dividing the gram weight of each infarct zone by the total weight of the infarct and expressing the result as a percent. The total weight of the infarct included the weights of the marginal, ischemic and necrotic core zones. Each sample was placed in a counting vial containing 10 percent formalin and analyzed in the gamma spectrometer. We then processed about 25 sections taken from the counting vials from each heart for conventional histologic studies, staining them with hematoxylin-eosin and Masson trichrome stains. We determined the extent of necrosis and hemorrhage in each. Standard criteria were used for necrosis (that is, the presence of cell infiltrates, cell disruption and fragmentation, fibroblastic proliferation and organizing scar). A metric grid was superimposed on the histologic slide to standardize determination of the extent of necrosis in each field.

The extent of hemorrhage was graded as follows: 0, hemorrhage not visible grossly or microscopically; 1, hemorrhage visible only microscopically and occupying less than 10 percent of each section; 2, hemorrhage visible grossly and microscopically occupying 10 to 25 percent of the section; 3, hemorrhage visible grossly and microscopically occupying 25 to 50 percent of the section; and 4, hemorrhage visible grossly and microscopically occupying 50 to 100 percent of the section.

TABLE III
Heart Rate and Aortic Flow After Occlusion (Groups 1 to 3) (mean ± standard error of the mean)

Time	Group 1	Group 2	Group 3
	Heart Rate After Occlusion (beats/min)		
C	105 ± 6†	86 ± 4	88 ± 3
5 min	110 ± 6†	90 ± 4	93 ± 6
2 hr	131 ± 6*†	90 ± 4	118 ± 7
6 hr	145 ± 7*	136 ± 5*	139 ± 5*
24 hr	172 ± 9*†	145 ± 5*	141 ± 6*
72 hr	129 ± 5*†	114 ± 4*	120 ± 5*
1 mo			80 ± 5
	Aortic Flow (ml/min) After Occlusion		
C	2935 ± 310	2064 ± 215	2200 ± 199
5 min	1980 ± 195*	2070 ± 243	2139 ± 245
2 hr	2096 ± 220*	1710 ± 190	2124 ± 234
6 hr	2030 ± 350*	2176 ± 217	2115 ± 230
24 hr	1419 ± 152*	2175 ± 237	1800 ± 216

* $P < 0.05$ compared with control value in the same group; † $P < 0.05$ comparing Groups 1 and 3 with Group 2.
C = control period before occlusion.

After the extent of hemorrhage was quantified for each section, a mean was obtained for each zone for each group.

Results

Occlusion Only (Groups 1 to 3)

Heart rate and aortic flow: Table III summarizes changes in heart rate and aortic flow for the groups with occlusion only. Aortic flow was significantly changed only in Group 1, the group later shown to have the largest infarcts. Heart rate was significantly elevated in all three groups 6 hours after occlusion and later. Mean aortic pressure in these groups revealed no consistent pattern of response to occlusion, although it did change markedly for short periods immediately after occlusion in some animals and after reperfusion in other animals. Microspheres were not given during these periods of fluctuating pressure.

Regional myocardial blood flow: Flow distribution to the histologically distinguished zones of the occluded left circumflex coronary arterial bed is summarized in Table IV. The weighted mean flow to the entire left circumflex coronary bed, measured with microsphere methods, was normalized to ml/min per 100 g for the bed. This is shown in Table IV as total left circumflex coronary flow. Five minutes after occlusion, greater flow ($P < 0.05$) reached the left circumflex coronary bed in Groups 2 and 3 than in Group 1. This was a result of a greater collateralization in the groups with long periods of instrumentation. In all groups there was a decrease in flow to the ischemic and core zones after 2 hours of occlusion and an increase flow in the jeopardized and marginal zones after 6 hours of occlusion. Flow in the left anterior descending artery tended to increase after occlusion. In Group 3, large standard errors of the mean were seen at 5 minutes in the ischemic and core zones (zones in which there was significant tissue loss at 1 month). About the same magnitude of flow was seen in each zone; that is, the greatest changes in flow were seen transmurally rather than between groups in the same zone.

Morphologic infarct characteristics: Table V shows the morphologic characteristics, including the extent of hemorrhage, of the infarcts observed in the animals with occlusion only (Groups 1 to 3). Of the three groups, Group 1 had the largest infarcts as measured from actual weight, percent of

TABLE IV
Regional Myocardial Blood Flow (ml/min per 100 g) After Occlusion (Groups 1 to 3) (mean ± standard error of the mean)

Myocardial Region	Time	Group 1	Group 2	Group 3
Jeopardized	C			64 ± 4
	5 min	44 ± 5	46 ± 3	40 ± 3*
	2 hr	56 ± 3*	51 ± 3*	
	6 hr	59 ± 3+	59 ± 3*+	
	1 mo			51 ± 5*†
Marginal	C			62 ± 4
	5 min	31 ± 2	35 ± 3	28 ± 8*
	2 hr	37 ± 2	40 ± 3	
	6 hr	39 ± 2	44 ± 3*	
	1 mo			40 ± 6*†
Ischemic	C			29 ± 10
	5 min	21 ± 2	28 ± 3	12 ± 3*
	2 hr	20 ± 3	27 ± 3	
	6 hr	15 ± 2+	20 ± 2*	
	1 mo			9 ± 2
Core	C			45 ± 12
	5 min	6 ± 0.05	8 ± 0.6	2 ± 2
	2 hr	4.5 ± 0.03	7 ± 0.6	
	6 hr	2.5 ± 0.03	4 ± 0.5*	
	1 mo			4 ± 2
LAD	C			61 ± 5
	5 min	99 ± 8	65 ± 5	69 ± 4
	2 hr	104 ± 6	73 ± 7	
	6 hr	120 ± 9†	78 ± 7	
	1 mo			57 ± 7
LCCM	C			52 ± 10
	5 min	24 ± 4	36 ± 4	38 ± 9
	2 hr	27 ± 2*	41 ± 3*	
	6 hr	27 ± 2†	45 ± 2*†	
	1 mo			46 ± 5*

* $P < 0.05$ compared with immediately preceding value;
† $P < 0.05$ compared with value at 5 minutes.
C = control before occlusion; LAD = left anterior descending coronary arterial flow determined with microsphere injection; LCCM = transmural left circumflex coronary blood flow determined with microsphere injection.

TABLE V
Infarct Characteristics in Dogs With Occlusion Only (Groups 1 to 3) (mean ± standard error of the mean)

	Group 1	Group 2	Group 3
Infarct size*			
LV (%)	29 ± 3	17 ± 2	8 ± 1
LCCA (%)	74 ± 3	44 ± 5	22 ± 1
Weight (g)	32 ± 2	18 ± 1	9 ± 1
Zone size†			
Jeopardized	0	0	0
Marginal	30 ± 5	57 ± 6	29 ± 3
Ischemic	18 ± 2	17 ± 2	21 ± 2
Core	49 ± 5	21 ± 3	51 ± 6
Zone size‡			
Jeopardized	11 ± 1	23 ± 2	36 ± 3
Marginal	10 ± 1	10 ± 1	3 ± 0
Ischemic	6 ± 1	3 ± 0	2 ± 0
Core	16 ± 2	4 ± 0	4 ± 0
Zone necrosis§			
Jeopardized	3 ± 0	2 ± 0	3 ± 0
Marginal	60 ± 8	55 ± 5	49 ± 7
Ischemic	91 ± 7	98 ± 8	95 ± 9
Core	96 ± 1	95 ± 1	100 ± 0
Hemorrhage‖			
Jeopardized	0	0	0
Marginal	1 ± 0	1 ± 0	0
Ischemic	2.6 ± 0.4	1.4 ± 0.4	0
Core	0	0	0

* Expressed as percent of left ventricular mass (LV), percent of left circumflex coronary arterial region (LCCA) and weight of infarct.
† Expressed as percent of weight of total infarct as determined by direct weight at time of necropsy.
‡ Expressed as weight in grams as determined by direct weight at time of necropsy.
§ Expressed as percent of total infarct as determined from histologic study.
‖ Graded from 0 to 4 as described under Methods.

total ventricular mass and percent of the left circumflex coronary bed. These differences were significant at the 5 percent level. In dogs in Group 1, the group with the least time for collateral development, the bulk of damage was in the necrotic core zone, which constituted 49 percent of the group's average infarct weight of 32 g. Most of the necrotic core zone was histologically severely damaged in all three groups. The necrotic core zone constituted 49 percent of the total infarct zone in Group 1 but only 21 percent of this zone in Group 2, in which collateral vessels had time to develop before occlusion. The pattern of damage in Group 2 (4 days of occlusion) resembled that of Group 3 (1 month of occlusion), although dogs in Group 3 had a larger jeopardized zone. Hemorrhage was present only in Groups 1 and 2 and was most severe in the ischemic zones.

Effect of collateral vessels on infarct size: To assess the effect of preexisting collateral vessels on infarct size in the groups with occlusion only, infarct size expressed as a percent of total left ventricular weight was correlated with collateral flow 5 minutes after occlusion in Groups 1 and 2. The correlation data ($r = 0.96$; $y = 49.1 - 1.32x$; $P < 0.05$) indicated that collateralization before occlusion was a major determinant of infarct size. Group 3 was excluded from this correlation because infarct size was influenced by tissue loss and scar contraction over the month-long observation period. In Groups 1 and 2 flow probe measurements made just before occlusion were compared with flow data in the left anterior descending coronary artery 5 minutes after occlusion. There was no significant difference between these values. Flow probe calculations were based on the weighed tissue in the left circumflex bed made at necropsy. In Group 3 flow probe data showed flows of 72 ± 10 ml/min per 100 g; flow assessed with microspheres averaged 52 ± 10 ml/min per 100 g.

Occlusion and Reperfusion (Groups 4 to 8)

Heart rate and aortic flow: Table VI summarizes changes in heart rate and aortic flow for the groups with both occlusion and reperfusion. Aortic flow remained similar in all five groups up to 6 hours but showed a significant decrease at 25 hours in Groups 6 and 7. Heart rates were significantly elevated in all groups after 3 hours, but the increase in heart rate was markedly less in Group 4 than in the other groups with reperfusion. Mean aortic pressure in the five groups did not respond consistently to occlusion, although it did change markedly for short periods immediately after occlusion in some animals. On reperfusion there were no significant changes in mean aortic pressure.

Regional myocardial blood flow distribution: Data from the five groups are shown in Table VII. Total flow returned within 1 hour of reperfusion, and there was *apparent* stabilization of total flow by 72 hours of reperfusion. The distribution of regional myocardial blood flow to the four zones of the formerly occluded vascular bed appears to follow the pattern of Groups 1 to 3 (occlusion only). Flows to the endocardial zones (core and ischemic) started to increase within the first hour of reperfusion, as did flows to the epicardial zones (marginal and jeopardized). However, by 72 hours of reperfusion, when total flow appeared to be stabilizing in control ranges, flows to the most epicardial zone (jeopardized) remained at its increased level, whereas there was a marked

TABLE VI
Heart Rate and Aortic Flow After Occlusion and Reperfusion (Groups 4 to 8) (mean ± standard error of the mean)

Time	Group 4	Group 5	Group 6	Group 7	Group 8
			Heart Rate (beats/min)		
C	87 ± 3	94 ± 4	83 ± 3	81 ± 4	87 ± 3
5 min	95 ± 3	99 ± 4	90 ± 4	90 ± 4	90 ± 3
3 hr	98 ± 4*	120 ± 5*	108 ± 4*	109 ± 5*	120 ± 4*
7 hr	121 ± 4*	177 ± 10*	137 ± 5*	135 ± 5*	152 ± 7*
25 hr	127 ± 4*	175 ± 11*	161 ± 6*	150 ± 6*	153 ± 8*
72 hr	110 ± 5*	125 ± 5*	121 ± 5*	119 ± 5*	122 ± 6*
1 mo	...	...	...	...	87 ± 5
			Aortic Flow (ml/min)		
C	2175 ± 217	2162 ± 274	2241 ± 186	2286 ± 315	2166 ± 314
5 min	2180 ± 236	2079 ± 317	2160 ± 137	2070 ± 238	2166 ± 218
3 hr	2185 ± 270	2160 ± 284	2160 ± 145	2180 ± 280	1920 ± 205
7 hr	2541 ± 314	2124 ± 289	1644 ± 195*	2160 ± 280	
25 hr	1980 ± 217	1925 ± 236	1452 ± 166*	1666 ± 179*	2448 ± 170
1 mo	...	...	...	...	2088 ± 130

* $P < 0.05$ compared with the control value in the same group.
C = control period before occlusion; 5 min = 5 minutes after occlusion; 3 hr = after 2 hours of occlusion and 1 hour of reperfusion; 7 hr = after 6 hours of occlusion and 1 hour of reperfusion; 25 hr = after 24 hours of occlusion and 1 hour of reperfusion; 72 hr = after 6 hours of occlusion and 72 hours of reperfusion; 1 mo = after 6 hours of occlusion and 1 month of reperfusion.

TABLE VII
Regional Myocardial Blood Flow (ml/min per 100 g) After Occlusion and Reperfusion (Groups 4 to 8) (mean ± standard error of the mean)

Myocardial Region	Group 4		Group 5		Group 6		Group 7		Group 8	
	Time	Flow	Time	Flow	Time	Flow	Time	Flow	Time	Flow
Jeopardized	5 min	39 ± 4	5 min	37 ± 4	5 min	38 ± 4	5 min	42 ± 3	C	40 ± 8
	3 hr	79 ± 3*	7 hr	89 ± 6	7 hr	83 ± 5	25 hr	90 ± 8	7 hr	41 ± 7*
	72 hr	82 ± 3†	72 hr	80 ± 7	72 hr	74 ± 7	72 hr	86 ± 8†	1 MR	59 ± 5*†
Marginal	5 min	32 ± 8	5 min	35 ± 3	5 min	35 ± 3	5 min	37 ± 4	C	32 ± 12
	3 hr	60 ± 3*	7 hr	82 ± 6*	7 hr	75 ± 6*	25 hr	71 ± 3*	7 hr	35 ± 7*
	72 hr	63 ± 3†	72 hr	53 ± 5*†	72 hr	63 ± 5†	72 hr	50 ± 7*†	1 MR	41 ± 5*†
Ischemic	5 min	22 ± 3	5 min	24 ± 4	5 min	29 ± 4	5 min	20 ± 3	C	25 ± 2
	3 hr	57 ± 5*	7 hr	71 ± 8*	7 hr	65 ± 5*	25 hr	41 ± 6*	7 hr	29 ± 4*
	72 hr	31 ± 4*†	72 hr	27 ± 4*	72 hr	30 ± 3*†	72 hr	12 ± 2*†	1 MR	8 ± 1*
Core	5 min	6 ± 2	5 min	4 ± 2	5 min	6 ± 0.05	5 min	3 ± 0.04	C	32 ± 6
	3 hr	7 ± 2	7 hr	4 ± 2	7 hr	7 ± 0.05	25 hr	4 ± 0.04	7 hr	13 ± 3
	72 hr	4 ± 2	72 hr	3 ± 2	72 hr	3 ± 1*†	72 hr	4 ± 0.04	1 MR	8 ± 1
LAD	5 min	69 ± 6	5 min	84 ± 6	5 min	72 ± 6	5 min	75 ± 6	C	70 ± 6
	3 hr	67 ± 5	7 hr	109 ± 6†	7 hr	89 ± 8*	25 hr	105 ± 7*	7 hr	111 ± 6*
	72 hr	74 ± 8	72 hr	90 ± 7	72 hr	84 ± 8	72 hr	84 ± 7	1 MR	68 ± 6*
LCCM	5 min	37 ± 4	5 min	28 ± 3*	5 min	34 ± 4	5 min	37 ± 2	C	35 ± 3
	3 hr	75 ± 6*	7 hr	78 ± 9*†	25 hr	77 ± 6*	25 hr	69 ± 5*	7 hr	36 ± 4
	72 hr	68 ± 6†	72 hr	51 ± 6	72 hr	63 ± 5*†	72 hr	59 ± 4*†	1 MR	49 ± 5*†

* $P < 0.05$ compared with the immediately preceding value.
† $P < 0.05$ compared with the value at 5 minutes.
LAD = left anterior descending coronary arterial blood flow determined with microsphere injection; LCCM = transmural left circumflex coronary blood flow determined with microsphere injection; MR = 1 month of reperfusion; other abbreviations as in Table VI.

redistribution away from the core and ischemic zones. The core zone was small in the groups with reperfusion (Table VIII). Therefore, the sustained return to control levels in the jeopardized and marginal zones as a result of reperfusion and the redistribution of flow away from the large ischemic zone are the predominant features reflected in Tables VII and VIII.

Morphologic infarct characteristics: Table VIII shows the morphologic characteristics, including the extent of hemorrhage, of the infarcts observed in Groups 4 to 8 (occlusion plus reperfusion). Dogs in Group 5, the group with the shortest interval for collateral development, had the largest infarcts, as assessed from actual weight, percent of total left ventricular mass and percent of the left circumflex coronary arterial bed. These differences were significant at the 5 percent level. Group 5 had the bulk of damage in the ischemic zone. In comparing data from Tables V and VIII the tissue salvage seen in Group 4 is a result of a decrease in size of both the ischemic and the core zones together with an increase in the size of the jeopardized zone. Reperfusion after more than 6 hours of occlusion (Groups 6 and 7) did not increase infarct size. Hemorrhage was present in both the ischemic and marginal zones of all groups. Its severity was greater in the ischemic zone and was greater than that observed in the groups with occlusion only (Table V).

Effect on infarct size of preexisting collateral vessels: To assess the effect of preexisting collateral development on infarct size in the groups with reperfusion, infarct size as a percent of total left ventricular weight was correlated with collateral flow at 5 minutes after occlusion in Groups 4 to 7.

TABLE VIII
Infarct Characteristics in Dogs With Occlusion and Reperfusion (Groups 4 to 8) (mean ± standard error of the mean)

	Group 4	Group 5	Group 6	Group 7	Group 8
Infarct size					
LV (%)	5 ± 3*	24 ± 4*	13 ± 2	17 ± 2	11 ± 1*
LCCA (%)	13 ± 4*	60 ± 7*	31 ± 4	46 ± 2	27 ± 1*
Weight (g)	6 ± 1*	26 ± 4*	13 ± 2	18 ± 2	12 ± 1*
Zone size (% total inf)[b]					
Jeopardized	0	0	0	0	0
Marginal	82 ± 5	20 ± 5	46 ± 5	19 ± 4*	27 ± 3*
Ischemic	9 ± 3*	76 ± 7*	48 ± 3*	71 ± 5	35 ± 4*
Core	9 ± 1*	4 ± 3*	6 ± 4*	10 ± 2*	39 ± 4*
Zone size (g)					
Jeopardized	36 ± 3*	17 ± 3*	30 ± 2*	21 ± 2	33 ± 3*
Marginal	4 ± 1*	5 ± 1*	6 ± 1*	3 ± 1*	3 ± 1
Ischemic	1 ± 0*	20 ± 3*	6 ± 1*	13 ± 1*	4 ± 1*
Core	1 ± 0*	1 ± 0*	1 ± 0*	2 ± 1*	5 ± 1*
Zone necrosis (%)					
Jeopardized	2 ± 0	4 ± 1	3 ± 0	5 ± 1	5 ± 2
Marginal	48 ± 7	54 ± 5	46 ± 5	56 ± 6	54 ± 3
Ischemic	88 ± 8	92 ± 8	82 ± 7	90 ± 9	95 ± 2
Core	95 ± 3	95 ± 5	96 ± 5	100 ± 0	100 ± 0
Hemorrhage					
Jeopardized	0	0	0	0	0
Marginal	1 ± 0	1 ± 0	1.4 ± 0.8*	1 ± 0	1 ± 0
Ischemic	3 ± 0.5*	3.8 ± 0.2*	3.6 ± 0.2*	2 ± 0	2 ± 0
Core	0.8 ± 0.7*	1 ± 0*	1 ± 0*	0	0

* $P < 0.05$ compared with Group 2.
Abbreviations as in Table I.

The correlation data ($r = 0.74$, $y = 45.2 - 1.7x$; $P < 0.05$) indicated that collateralization before occlusion and reperfusion was a determinant of infarct size but a considerably and significantly ($P < 0.05$) lesser factor than in the groups with occlusion only. Group 8 was excluded from this correlation because infarct size was influenced by tissue loss and scar contraction over the month-long observation period.

Flow probe versus microsphere flow measurements: Flow probe measurements in reperfused tissue in Groups 4 to 7 after 1 hour of reperfusion averaged 88 ± 11 ml/min per 100 g, whereas microsphere flow data averaged 75 ± 10 ml/min per 100 g. After 3 days of reperfusion there was similar agreement between flow probe and microsphere flow values. In Group 8 flow probe values (62 ± 12 ml/min per 100 g in the control period) were significantly different ($P < 0.05$) from microsphere flow values (35 ml/min per 100 g) determined 1 month later. After 1 hour of reperfusion flow probe values averaged 57 ± 8 ml/min per 100 g compared with the microsphere value of 36 ± 4 ml/min per 100 g ($P < 0.05$). There was only one flow probe measurement after 1 month of reperfusion; this showed a value of 55 ml/min per 100 g compared with 51 ml/min/100 g by microsphere measurements.

Experiments to determine optimal microsphere procedures: Data from experiments to determine optimal microsphere procedures and possible loss from ischemic myocardium are presented in Table II. Group A is a control group of dogs with normal tissue from both the left circumflex and left anterior descending arterial beds compared 3 days after microsphere injection. There was a small but significant difference ($P < 0.05$) between the endocardial and epicardial ratios between these two beds in this group without occlusion. Dogs in Group B showed a small but significant ($P < 0.05$) loss of microspheres in both the endocardium and the epicardium of the ischemic left circumflex bed. When sample size was increased (Group C), there was no significant loss of microspheres in the ischemic zone. When the number of microspheres injected was increased (Group D), the data indicated that microsphere loss in ischemic tissue after 2 to 4 days of occlusion is minimal even when sample size is small. Experimental Group 3 (animals with 1 month of occlusion) had a substantial loss of tracer microspheres in the endocardium (about 50 percent) and a small loss (about 15 percent) in the epicardium of the ischemic myocardium. Results in Group 8 were similar, indicating no additional microsphere loss with reperfusion.

Discussion

This study confirms and extends our earlier observations[3] and those of Herzel et al.[1] showing that blood flow within a developing myocardial infarct is redistributed during the first few hours of occlusion. These observations are extended to the reperfused myocardial infarct. We found that total and regional reflow measured soon after reperfusion were poor predictors of the extent of tissue salvage because at 1 hour of reperfusion relatively high levels of reflow occur in tissues that are already undergoing necrosis. Thus, the extent of collateral circulation existing at the time of occlusion is a major determinant of the size of the ensuing infarct after both permanent occlusion and reperfusion.

Because identifying tissue was important in this study, we showed that a myocardial infarct 3 or 4 days after occlusion has a definite structure and can be separated into reproducible zones in both the nonreperfused and reperfused myocardium. The borders of the tissue perfused with radiolabeled and normal blood were closely matched to the dye delineators, so that only a small area of slightly contaminated tissue was present in the jeopardized zone. Herzel et al.[1] showed that the

amount of contamination could be predicted with this method, and we verified this finding. Rivas et al.[2] confirmed that myocardial infarcts in the dog are heterogeneous, and that the relation between blood flow and the extent of a myocardial infarct can be determined only by comparing regional blood flow measurements with histologic assessment of the extent of the infarct. Thus, we employed this technique in our study.

Correlation between extent of myocardial necrosis and regional blood flows early after coronary occlusion: Our results in the permanently occluded myocardium resemble those of Rivas et al.[2]; that is, we found a high correlation between the regional blood flows during the first few hours after occlusion and the extent of necrosis seen several days later. However, when this concept was extended to the reperfused myocardium, the relation became more complicated. We found that high levels of reflow in the marginal tissue early in reperfusion may indeed predict viable tissue several days later. But a similar flow to layers slightly more endocardial may be perfusing tissue that is already necrotic. Therefore, the early level of reflow as such will not predict future tissue viability. Jennings et al.[13] showed that the posterior papillary muscle is subject to irreversible damage after a short period of ischemia and is poorly reperfused, if at all. Our observations were similar, but we found that the "no-reflow" (core) zone was quite small, about 0.5 to 1.5 g of tissue and that the ischemic zone, which was reperfused with reflow, was several times this size. Where this high level of reflow occurs in necrotic tissue, hemorrhage is likely. The most extensive hemorrhage was seen in the ischemic zone tissue in Groups 5 and 6. These were the groups subjected to occlusion for 6 hours. Hemorrhagic infarcts after 5 hours of occlusion and reperfusion have previously been reported.[14]

We tested the hypothesis that coronary collateral vessels may enlarge in dogs that are chronically instrumented for several weeks. This is demonstrated by the differences between ischemic and collateral flow in Groups 1, 2, 5 and 6. The dogs with the longest interval between instrumentation and occlusion had the smallest infarct size seen in each group. Bloor[15] has reported that collateral vessels may be influenced by chronic instrumentation.

Willerson et al.[16] stated that 3 minutes after regional reperfusion preceded by 2 hours of occlusion, the level of flow in animals on a right heart bypass is somewhat higher than that we found after 1 hour of reperfusion. We allowed 1 hour of reflow to occur before measuring regional myocardial blood flow. It is likely that our original reflow value would have been higher immediately after reperfusion because our flow probe measured a 35 percent greater flow immediately after reperfusion than that measured 1 hour later with both flow probe and tracer microspheres. This early high reflow level is a result of reactive hyperemia.[6] It is likely that both reactive hyperemia and a redistribution of flow occur simultaneously and that both events could contribute to changes of flow with time after reperfusion. Our data suggest that the initial amount of collateral flow received by the ischemic myocardium together with the work demand on the myocardium at the time are the most important predictors of subsequent tissue viability.

Estimates of collateral flow necessary to prevent necrosis and effect of reflow: To stabilize oxygen consumption, considerable effort was made in preparing a standard model for these experiments. However, severe tachycardia occurred after both occlusion and reperfusion. This increase in heart rate influenced myocardial oxygen demands, as can be seen in the changes in the nonischemic blood flow. As heart rate increased so did the nonischemic regional flow ($r = 0.84$). Because we quantitated the collateral flow in various zones of the myocardium after occlusion and the amount of necrosis in these zones, we can make approximations of the innate collateral flow necessary to prevent necrosis and the amount of flow that may be considered marginal. These estimates would apply only to the oxygen demands of the myocardium under these particular hemodynamic situations. If the normal zone flow is representative of myocardial oxygen demands then this flow, averaging 85 ml/min per 100 g, can be considered a rough index of myocardial metabolic demand. We found that blood flow of less than 30 ml/min per 100 g resulted in large amounts of necrotic tissue, particularly in the endocardium, where metabolic demands may be high. Flow of 30 to 45 ml/min per 100 g may be marginal, depending on the demand, and an intermittent amount of necrosis was found in these regions. Where the initial blood flow was greater than 45 ml/min per 100 g, almost no necrosis resulted. Reflow instituted after 6 hours or more of occlusion will not salvage ischemic tissue. Indeed, reflow to these zones may accelerate the damage by hemorrhage. In our study, a significant amount of tissue was salvaged only in the group with reperfusion after a 2 hour occlusion (Group 4). Only in this group was there less systemic hemodynamic deterioration than in the control group; this finding is similar to that of other reports[14,17,18] of serious deterioration after reperfusion. The liberal use of procainamide may have stabilized the condition of these Group 4 dogs, diminishing deterioration; that is, the frequency and severity of arrhythmias may have been sufficiently reduced to decrease infarct size. In animals undergoing reperfusion after 6 hours of occlusion, we saw significant hemodynamic disturbances and hemorrhagic infarcts, similar to those reported by others.[14] Apparently, after 24 hours of occlusion and reperfusion (Group 7), the effects of reperfusion were less evident. Tissue was not salvaged, but the hemodynamic deterioration was not evident and the amount of hemorrhage seen was less than that in Groups 4 to 6.

The concept of marginal and jeopardized zones: From this detailed analysis of flow to the various regions of infarction, it is apparent that the concept of marginal tissue may have to be reconsidered. After the initial occlusion, collateral flow follows a reasonably linear flow gradient from the epicardium to the core of the infarct, with the redistribution of flow occurring within the developing infarct within the first few hours. The flow

is then nonlinear. It seems that the majority of the flow goes to the noninfarcted jeopardized zone, while a rapidly narrowing band of tissue may have an intermittent range of flows, and in the largest part of the infarct flows will be very low. These changes appear to occur within the first few hours of occlusion and are very evident after several days. One month after occlusion we verified the finding of a very narrow marginal zone. The possibility of a very narrow border region in the dog infarct was suggested by Schaper and his co-workers[19,20] and others.[15,21] It appears that once a critical level of decreased flow is reached, the infarct may be self-perpetuating because vessels are no longer able to carry flow, either collaterally or with reperfusion. The integrity of the vessel after occlusion may be of critical importance.[22] The redistribution of flow away from the developing infarct may provide flow to more superficial layers, but the narrowing of the marginal zone limits within a few hours the potentially salvageable tissue. To salvage myocardium after occlusion, myocardial demands must be reduced, collateral channels must enlarge and vessels must be prevented from disrupting, thus shifting the marginal zone to the jeopardized zone.

Although we did not measure the flow gradient across the jeopardized zone, the difference between large and small infarcts (Groups 1 and 2) depended primarily on the size of this zone. Small infarcts were mainly a result of an increase in the jeopardized zone rather than a decrease in the size of the left circumflex arterial beds at risk. In our experiments left circumflex arterial bed size ranged from 26 to 45 percent of left ventricular mass but in the majority of dogs was approximately 37 percent of ventricular mass. When the range of the size of the arterial beds is narrow then the degree of collateralization would be the predominant factor in infarct size. However, a wide variation in the size of the beds at risk could be a major factor in determining infarct size, as has been reported.[23] In our experiments small infarcts tended to be patchier than large infarcts and manifested a greatly extended jeopardized zone. The flow to this zone was similar in all experiments; thus, it appears that increases in collateral flow tend to increase the size of the jeopardized zone rather than to increase flow to that zone. It seems likely that for tissue to be classified as marginal or potentially salvageable, a relatively high level of flow of at least 30 ml/min per 100 g is critical. Future studies should carefully assess the biochemical, mechanical and hemodynamic characteristics of the jeopardized and marginal zones if therapeutic interventions are to increase marginal flow or reduce the region's need for flow.

Because of technical limitations, most studies have necessarily reported average values when grossly normal and grossly abnormal tissues interdigitate. Kirk et al.[12] reported that the flow level may be high or low on either side of a narrow markedly interdigitating border zone. Our data also suggest that this is true once severe necrosis is present. It is possible that this narrow margin may have some movement transmurally. Therefore, the true character of both the marginal and the border zones remains to be detailed.

It is also unlikely that tissue sampling can be completely unambiguous, even in well defined infarct zones, because some infarcts may be patchy. Sampling of several transmural layers when ambiguity exists seems the best alternative.[2] Because both sampling methods and inherent flow assessments lead to averaging, the sharp boundaries that may exist in infarcts are likely to be missed after both occlusion and reperfusion.

By measuring infarcts in dogs after 1 month of occlusion, we assessed the effect of tissue loss on regional blood flow. Our data suggest that nearly half of the original infarct was lost because of scar retraction. Theroux et al.[24] made a similar finding using ultrasonic dimension gauges in animals with long-term occlusion and reperfusions. Because of the tissue changes in these long-term studies, it is unlikely that flow calculated from the earliest injections of microspheres will be accurate. This can be seen in the large standard error of the mean in flow values in the core zones in Groups 3 and 8 during the control period.

Accuracy of microsphere flow measurements: It is apparent from Table II that microsphere loss in ischemic tissue may be detectable (about 10 percent) within 2 to 4 days. The reason for this loss is obscure because significant tissue loss is not evident either grossly or histologically at this time. Increasing the sample size or the number of microspheres injected increases counting efficiency. The number of microspheres in 1 g of tissue when 2×10^6 microspheres are injected is about 500; this approximates the level at which regional flow measurements may have large errors.[25] By increasing the number of microspheres injected these errors may be minimized not only in the region of reduced flow but also in normal zones or regions that were normal at the time of earlier injections but later became ischemic. The accuracy of these measurements will depend on the number of samples taken through the zone and on the number of microspheres found in small samples.[25] As sample size gets smaller and when blood flow per unit mass of tissue is very small, the accuracy of the measurement becomes suspect.[25] We injected large numbers (6×10^6) of microspheres in these studies. Even so, it is unlikely that results of tissue samples of less than 0.5 g or flow levels lower than 10 ml/min per 100 g would have a high degree of accuracy. Millard et al.[26] showed that the problem of an adverse response to microspheres is related to the use of Tween 80® as a surface active agent rather than to the microspheres themselves. We observed the response reported by Millard et al. in about 15 percent of animals and never a second time in the same animal. These animals were always allowed to return to control conditions before further experiments were carried out. It is nevertheless possible that the large number of microspheres may have affected normal tissue.

A close scrutiny of the histologic findings from normal zones showed no alterations that would occur if a significant number of capillaries were occluded. In animals

subjected to 1 month of occlusion or to occlusion and 1 month of reperfusion, significant amounts of microspheres were lost, primarily from the endocardial regions. The loss of microspheres can be explained by the flow probe data because these data are based on tissue weights at the time of necropsy. Because flow probe measurements showed significantly greater flow than that shown by the earlier injection of microspheres, one might conclude that the microsphere loss comes as a result of tissue loss. However, this loss does not alter the conclusions in the 1 month studies because whether the tissue flow is 2 or 8 ml/min per 100 g is not critical, because both levels are well below that necessary to sustain cardiac viability. It is not clear whether there is significant microsphere loss in marginal tissue subjected to long-term occlusion. Thus, accurately determining the amount of marginal tissue existing at any one time and the range of flows that denote marginal tissue may be difficult in long-term experiments where there may be microsphere loss from earlier injections. However, there is no evidence that microsphere data may be inaccurate for necrotic tissue in which microspheres are not subject to loss due to tissue loss.

The dogs in group 8 were likely to have hemorrhagic infarcts because they had 6 hours of occlusion before reperfusion. These dogs had infarcts that were still hemorrhagic after 1 month, and the tissue loss was less than that in Group 3. The consequences of the retention of a large hemorrhagic scar are unknown.

The determination of blood flow to the revascularized heart, as has been measured clinically,[27] should be done with the knowledge that the volume of early flow into ischemic regions of the heart may not correlate well with flow determined later. This disparity may be a result of redistribution and reactive hyperemia in the reperfused tissue.

References

1. **Hirzel HO, Nelson GR, Sonneblick EH, et al:** Redistribution of collateral blood flow from necrotic to surviving myocardium following coronary occlusion in the dog. Circ Res 39:214–222, 1976
2. **Rivas F, Cobb FR, Bache RJ, et al:** Relationship between blood flow to ischemic regions and extent of myocardium infarction. Circ Res 38:439–447, 1976
3. **Bishop SP, White FC, Bloor CM:** Regional myocardial blood flow during acute myocardial infarction in the conscious dog. Circ Res 38:429–438, 1976
4. **Kloner RA, Reimer KA, Jennings RB:** Distribution of coronary collateral flow in acute myocardial injury: effect of propranolol. Cardiovasc Res 10:81–90, 1976
5. **Maroko PR, Libby P, Ginks WR, et al:** Coronary reperfusion. I. Early effects on local myocardial function and the extent of myocardial necrosis. J Clin Invest 51:2710, 1972
6. **Bloor CM, White FC:** Coronary artery reperfusion: effects of occlusion duration on reactive hyperemia responses. Basic Res Cardiol 70:148–158, 1975
7. **Bloor CM, White FC, Sobel SE:** Coronary and systemic effects of prostaglandins in the unanesthetized dog. Cardiovasc Res 7: 156–166, 1973
8. **Rudolph AM, Heymann MA:** The circulation of the fetus in utero. Methods for studying distribution of blood flow. Circ Res 21: 163–184, 1967
9. **Capurro NL, Goldstein RA, Aamodt R, et al:** Microsphere loss from infarcted myocardium: an important technical limitation (abstr). Circulation 56: Suppl III: III-350, 1977
10. **Jugdutt B, Becker L:** Microsphere loss from necrotic myocardium after experimental coronary artery occlusion (abstr). Circulation 56: Suppl III: III-341, 1977
11. **Eckstein RW:** Effects of exercise and coronary artery narrowing on coronary collateral circulation. Circ Res 5:230–235, 1957
12. **Kirk ES, Hirzel HO, Sonnenblick EH:** The size of infarcts: anatomical limits and transmural extent (abstr). Circulation 56: Suppl III: III-267, 1977
13. **Kloner RA, Ganote CE, Jennings RB:** The "no-reflow" phenomenon after temporary coronary occlusion in the dog. J Clin Invest 54:1496–1508, 1974
14. **Bresnahan GE, Roberts R, Shell WE, et al:** Deleterious effects due to hemorrhage after myocardial reperfusion. Am J Cardiol 33:82–86, 1974
15. **Bloor CM:** Coronary artery reperfusion. In, Current Topics in Coronary Research: Advances in Experimental Medicine and Biology, Vol 39. New York, Plenum Press, 1973, p 297
16. **Willerson JT, Watson JT, Hutton I, et al:** Reduced myocardial reflow and increased coronary vascular resistance following prolonged myocardial ischemia in the dog. Circ Res 36:771–781, 1975
17. **Lang TW, Corday E, Gold H, et al:** Consequences of reperfusion after coronary occlusion. Effects on hemodynamic and regional myocardial metabolic function. Am J Cardiol 33:69–81, 1974
18. **Mathur VS, Guinn EA, Burris WH:** Maximal revascularization (reperfusion) in intact conscious dogs after 2 to 5 hours of coronary occlusion. Am J Cardiol 36:252–261, 1975
19. **Flameng W, Wilsten B, Wimpler B, et al:** Influence of perfusion pressure and heart rate on local myocardial flow in the collateralized heart with chronic coronary occlusion. Am Heart J 89:51–59, 1975
20. **Pasyk S, Schaper W:** Influence of collateral flow on the ischemic tolerance of the heart following acute and subacute coronary occlusion. Circulation 53:Suppl I:I-57–I-62, 1976
21. **Smith HJ, Singh BN, Norris RM, et al:** Changes in myocardial blood flow and S-T segment elevation following coronary artery occlusion in dogs. Circ Res 36:697–705, 1975
22. **Ashraf M, Livingston L, Bloor CM:** Ultrastructural alterations in myocardial vessels after coronary artery occlusion. In, Scanning Electron Microscopy. Chicago, ITT Research Institute, 1977, p 501
23. **Lowe JE, Reimer KA, Jennings RB:** Experimental infarct size as a function of the amount of myocardium at risk. Am J Pathol 90: 363–380, 1978
24. **Theroux P, Ross J Jr, Franklin D, et al:** Coronary arterial reperfusion. III. Early and late effects on regional myocardial function and dimensions in conscious dogs. Am J Cardiol 38:599–606, 1976
25. **Buckberg GD, Luck JC, Payne DB, et al:** Some sources of error in measuring regional blood flow with radioactive microspheres. J Appl Physiol 31:598–604, 1971
26. **Millard RW, Baig H, Vatner SF:** Cardiovascular effects of radioactive microsphere suspensions and Tween 80 solutions. Am J Physiol 232: H331–H334, 1977
27. **Kreulen TH, Kirk ES, Gorlin R:** Coronary artery bypass surgery: assessment of revascularization by determination of blood flow and myocardial mass. Am J Cardiol 34:129–135, 1974

Servocontrolled Cardiac Assistance: Effects of Left Ventricular to Aortic and Left Atrial to Aortic Assistance on Infarct Size

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Devices for cardiac assistance are effective in supporting the failing circulation. In this study the effect of left ventricular to aortic assistance in salvaging ischemic myocardium was evaluated in dogs and compared with the effect of left atrial to aortic assistance. In a control group, there was good correlation between measurements of infarct size obtained with S-T segment mapping at 20 minutes, triphenyl tetrazolium chloride staining at 5 hours and determination of the distribution of radioactive microspheres ($P < 0.01$). A servocontrolled roller pump used to control pump speed according to left atrial pressure allowed reduction of left ventricular pressure to 38 percent of systemic levels and provided stable bypass for prolonged periods. The pressure-time index was reduced to 37 percent of baseline levels ($P < 0.005$). A reduced infarct size, as measured with S-T segment mapping and triphenyl tetrazolium chloride staining, was observed in Group II, dogs given left ventricular to aortic assistance before occlusion of the left anterior descending coronary artery ($P < 0.05$), and in Group III, dogs given assistance 20 minutes after occlusion ($P < 0.05$). Left atrial to aortic assistance did not reduce infarct size in this model. Electron microscopic studies confirmed the infarct distribution. Blood flow distribution measured with use of radioactive microspheres showed that in the ischemic area endocardial/epicardial ratio increased with left ventricular assistance; in the control group and with left atrial assistance the ratio decreased with the second occlusion ($P < 0.05$). Left ventricular to aortic assistance is thus superior to left atrial to aortic assistance in ability to salvage ischemic myocardium. The servocontrolled roller pump offers an effective, simple method of postoperative cardiac assistance.

Cardiogenic shock after cardiac surgery may be unresponsive to intraaortic balloon counterpulsation. Devices for circulatory assistance have been shown to be effective in supporting the circulation in this situation. Some current systems bypass the failing left ventricle using a simple roller pump from the left atrium[1–3] or from the left ventricular apex[4,5] to the aorta. Others utilize an auxiliary ventricle from the left ventricular apex to the aorta.[6,7] In addition to supporting the circulation, cardiac assistance may result in the salvage of ischemic myocardium by increasing the oxygen supply/demand ratio.[8,9] Previous studies[10] have shown that left ventricular to aortic assistance is more effective than left atrial to aortic assistance in reducing myocardial oxygen consumption. Pennock et al.[11] showed that the effectiveness of different degrees of left ventricular assistance was dependent on the size of the infarct. In their group with a large infarct only very high degrees of bypass were effective in reducing infarct size. In their small infarct model, lesser degrees of bypass were effective in reducing S-T segment elevation. A previous study from our laboratory[12] showed that left atrial to aortic assistance effectively reduced infarct size in a small infarct model, but not in the large infarct model.

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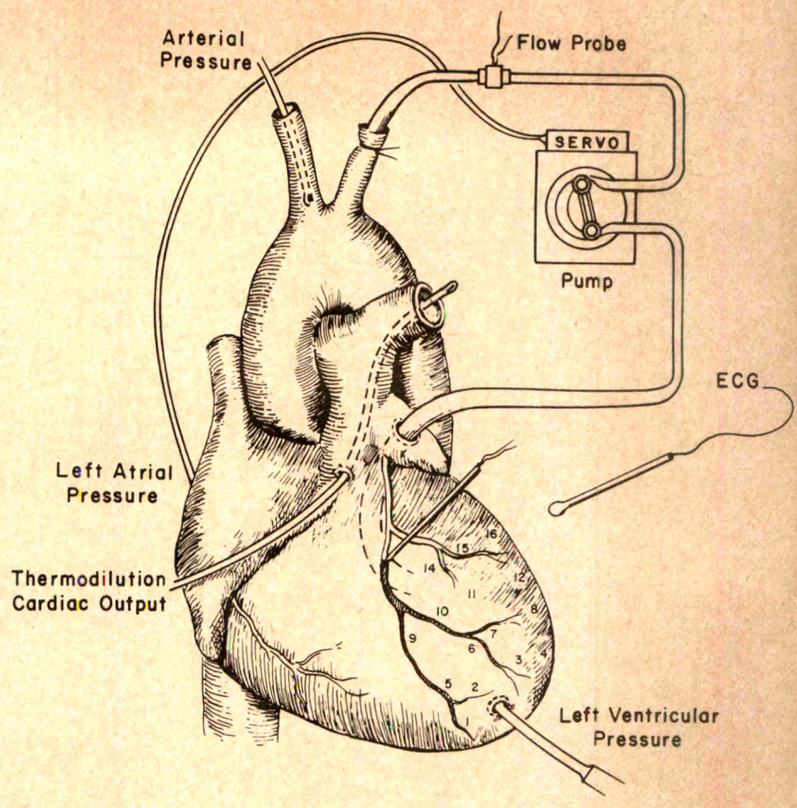

FIGURE 1. Cannulation for study of the effects of left ventricular to aortic assistance on infarct size. The left ventricular cannula is passed by way of the left atrial appendage into the left ventricular cavity. The numbered points, about 1 cm apart, are the sites used for S-T segment mapping and subsequent measurement of radioactive microsphere distribution and electron microscopy. ECG = electrocardiogram.

A high degree of bypass is required to effect a significant reduction in oxygen consumption.[10,13–16] This can be difficult to achieve with a roller pump because of the danger of cavitation and air embolism. A servocontrol mechanism was therefore developed to control a roller pump according to the left atrial pressure, which is effective for both left atrial to aortic assistance[3] and left ventricular to aortic assistance.[12] This study compared the effects on infarct size of servocontrolled left ventricular to aortic assistance with the previously reported effects[12] of left atrial to aortic assistance.

Methods

Experimental groups: Twenty-five mongrel dogs weighing 17 to 26 kg were studied. In Group I, seven control dogs, results of two 20 minute occlusions of the proximal left anterior descending coronary artery were compared, and infarct size at 5 hours was correlated with data from the S-T segment map, radioactive microsphere distribution and triphenyl tetrazolium chloride staining.[17] In Group II, seven dogs, results of a control occlusion were compared with results of an occlusion instituted after 5 hours of left ventricular to aortic assistance. In Group III, six dogs, only one occlusion was performed and left ventricular to aortic assistance was instituted after 20 minutes of ischemia. The results in these groups are compared with the previously reported results of left atrial to aortic assistance.[12] The experimental design and methods used were similar to those used in the previous study except for the placement of the cannulas.

Procedures: The dogs were anesthetized with sodium pentothal, 25 mg/kg, intubated and ventilated with a controlled volume respirator. Blood gases were monitored and the respirator was adjusted to maintain partial pressure of oxygen at about 100 mm Hg, partial pressure of carbon dioxide at 30 to 35 mm Hg and pH at 7.35 to 7.40. The heart was exposed through a median sternotomy and was suspended in a pericardial cradle. The internal mammary artery was cannulated for arterial pressure monitoring and the left atrium for pressure monitoring and injection of radioactive microspheres. The left ventricle was cannulated at its apex with a rigid cannula to measure left ventricular pressure and contractility (Fig. 1). The dogs were heparinized with 3 mg/kg body weight and supplementary doses of 2 mg/kg of heparin every 2 hours.

The left anterior descending coronary artery was dissected and snared at the junction of its proximal and middle thirds proximal to a major apical branch. Dogs whose coronary arterial anatomy did not conform to the basic distribution described were rejected. A heavy silk snare was passed around the vessel. Fifteen to 20 points for S-T segment mapping of the epicardium were chosen (Fig. 1); the points lay in four horizontal rows 1 cm apart, each point separated by about 1 cm. Epicardial electrocardiograms were obtained using a cotton-tipped electrode. The standardization was adjusted so that 1 mv caused a 1 mm deflection; S-T segment elevation of 2 mm was considered significant. The number of points with significant elevation was recorded (nST) and a mean elevation ($\overline{ST}$) computed.

Arterial pressure, left ventricular pressure and its first derivative (dP/dt) were recorded on a Brush recorder. The pressure-time index, calculated by multiplying the mean left ventricular pressure by the duration of the ventricular curve per minute, was expressed in mm Hg/sec per min. Esophageal

temperature was monitored and a heating pad used to keep the temperature at 35 to 37° C. The surface of the heart was kept warm with moist pads at 37° C.

Group I (seven control dogs): After baseline measurements were obtained, the coronary artery was snared. Electrocardiograms were obtained every 5 minutes for 20 minutes. At 18 minutes 4 million units of strontium-85–labeled microspheres (15 μ) was injected into the left atrium over 20 seconds, and the line was flushed with 10 ml of saline solution. Release of the snare at 20 minutes was followed by a recovery period of 1 hour during which surface electrocardiograms were obtained every 20 minutes. The coronary artery was then snared for a second occlusion in the same location. Surface electrocardiograms were obtained every 5 minutes for 20 minutes. At 18 minutes 4 million units of cerium-141–labeled microspheres (15 μ) was injected in a similar fashion into the left atrium. The dogs were then kept in stable condition for 5 hours with the artery occluded. Arterial gases and pH were monitored each hour and corrected as necessary. The hematocrit was measured hourly and kept stable with blood transfusions and infusion of Ringer's lactate solution. Surface electrocardiograms were obtained every hour. Five hours after

TABLE I

Effects of Left Ventricular to Aortic Assistance on Hemodynamics

	Group I: Controls (1st 20 min/ 2nd 20 min)		Group II: Two Occlusions (1st 20 min/ 2nd 20 min)		Group III: Delayed Assist (20 min occl/ 20 min assist)		La-A Assist (1st 20 min/ 2nd 20 min)	
Mean arterial pressure (mm Hg)	118 ±7	118 ±8	119 ±9	106 ±7	93 ±6	86 ±6	114 ±6	107 ±5
Pulse rate (beats/min)	141 ±4	151 ±4	165 ±8	154 ±10	179 ±12	165 ±12	156 ±7	152 ±10
Systolic LV pressure (mm Hg)	135 ±10	132 ±7	131 ±13	41 ±11‡	110 ±5	47 ±6†	137 ±6	123 ±3*
Cardiac output (liters/min)	...	...	...	...	...	...	2.2 ±0.3	2.1 ±0.2
Pump flow (liters/min)	...	...	0	1.71 ±0.12	2.3 ±0.22	1.8 ±0.20	...	1.8 ±0.2
Percent bypass	...	...	0	100	100	100	...	86
Pressure-time index (mm Hg/sec per min)	3518 ±438	3360 ±286	3795 ±1202	1395 ±886†	3707 ±957	1913 ±1134†	4069 ±236	3442 ±347*

* $P < 0.05$.
† $P < 0.005$.
La-A Assist = left atrial to aortic assistance; LV = left ventricular.

TABLE II

Effect of Left Ventricular to Aortic Assistance on Infarct Size and Blood Flow Distribution

	Group I: Controls (1st 20 min/ 2nd 20 min)		Group II: Two Occlusions (1st 20 min/ 2nd 20 min)		Group III: Delayed Assist (20 min occl/ 20 min assist)		La-A Assist* (1st 20 min/ 2nd 20 min)	
nST	8.0 ±0.8	7.2 ±0.6	10.0 ±0.98	7.3 ±1.7	9.6 ±1.44	4.4 ±1.54†	8.5 ±0.7	7.9 ±0.7
$\overline{ST}$	6.3 ±0.9	5.9 ±1.1	6.5 ±0.80	4.5 ±0.61†	6.6 ±0.96	4.4 ±0.46†	5.9 ±0.8	6.5 ±0.9
nST × $\overline{ST}$	51.4 ±10.4	45.2 ±11.9	66.6 ±11.2	38.2 ±12.7†	65.0 ±15.84	21.4 ±8.18†	52.9 ±11.3	51.5 ±10.4
Infarct weight‡ (g/100 ml)	...	14.5 ±1.4	...	9.98 ±1.31	...	10.8 ±1.43	...	11.6 ±1.6
Endo/Epi ratio								
Normal area	1.08 ±0.05	1.11 ±0.06	1.05 ±0.02	1.16 ±0.05*	1.02 ±0.01	1.03 ±0.01	1.11 ±0.07	1.03 ±0.04
Ischemic area	0.69 ±0.05	0.43 ±0.05†	0.65 ±0.07	0.82 ±0.06†	0.59 ±0.06	0.75 ±0.04†	0.66 ±0.04	0.48 ±0.10†

* The effects of left atrial to aortic (La-A) assistance on infarct size and myocardial blood flow distribution, as previously reported,[12] are shown in this column.
† $P < 0.05$.
‡ As determined with triphenyl tetrazolium chloride staining at 5 hours.
__assist = assistance; endo/epi ratio = endocardial/epicardial ratio; nST = number of points with S-T elevation greater than 2 mv; occl = occlusion; ST = mean elevation of S-T segments.

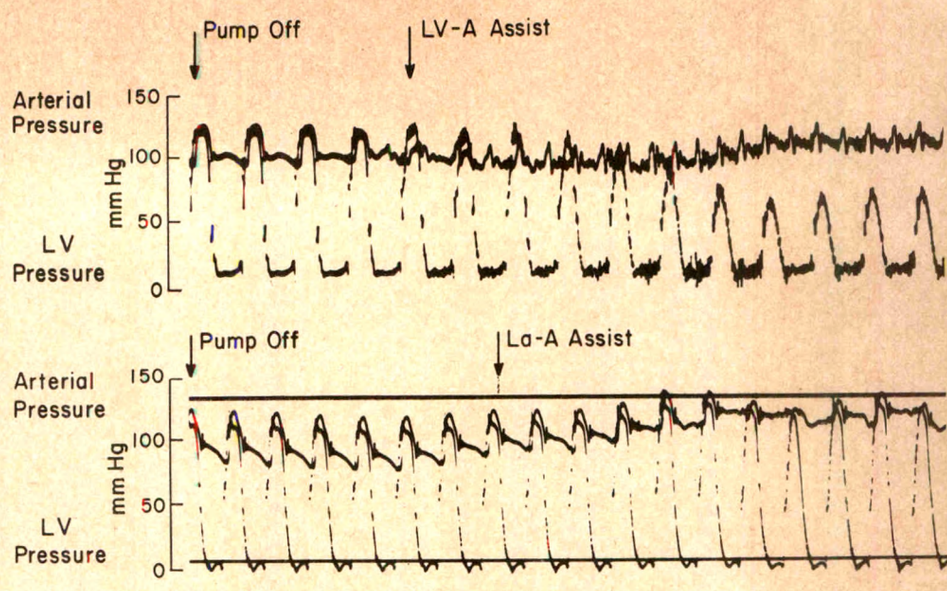

FIGURE 2. Effect of servocontrolled cardiac assistance on simultaneous arterial and left ventricular (LV) pressures. Left atrial to aortic (La-A) assistance does not reduce left ventricular pressure below systemic levels; left ventricular to aortic (LV-A) assistance effectively reduces left ventricular pressure to more than 50 percent below arterial pressure.

the second occlusion, the heart was rapidly excised and immersed in iced saline solution. The heart was sliced in 1 cm thick rings, each containing a row of epicardial marking sutures (Fig. 1). Biopsy specimens were taken from each epicardial site and from the adjacent normal myocardium in the rings involved by the infarct. These were submitted for histologic and electron microscopic studies. The rings were then incubated for 10 minutes in a warm solution (37° C) containing triphenyl tetrazolium chloride, as described by Lie et al.[17] The infarct was delineated as a gray area; the surrounding normal area was a brick-red color. The unstained area was weighed separately and the result expressed as a percent of left ventricular weight. A correction was made for areas that showed only a patchy infarct. Biopsy specimens were taken for electron microscopic studies from each S-T site, from the center of the triphenyl tetrazolium chloride-delineated infarct, from the margin and from the normal area. A tracing was made of the infarct distribution. Each ring was then sliced into segments, each about 1 cm square to include one epicardial marking suture, and divided into epicardial and endocardial portions; the right ventricle was submitted separately. Radioactivity was measured in a Picker gamma scintillation counter for 7 minutes. The results were expressed as a percent of the nonischemic area in counts/g and the epicardial/endocardial and cerium/strontium ratios were computed.

Group II (left ventricular to aortic assistance before occlusion, seven dogs): A similar procedure was followed in Group II, but left ventricular to aortic assistance was instituted before the second occlusion. The left ventricle was cannulated by way of the left atrial appendage with a large bore venous cannula, with drainage holes in both the left ventricle and the left atrium; the blood was reinfused through a cannula in the carotid artery. A single head roller pump was used for assistance. The servomechanism previously described[3] adjusted the pump speed according to the atrial pressure. In these seven experiments left ventricular to aortic assistance was instituted just before the second occlusion and continued for 5 hours. At 1 hour, assistance was discontinued for 5 minutes, and the effect on the S-T segment map was evaluated.

Group III (left ventricular to aortic assistance after occlusion, seven dogs): In this group, only one occlusion was used, and left ventricular to aortic assistance was instituted after 20 minutes of occlusion. The injection of microspheres was made into the left ventricular catheter rather than into the left atrium while the dogs were on left ventricular to aortic assistance. During this time total bypass was achieved and an attempt made to reduce the left ventricular pressure to approximately 50 percent of the arterial pressure.

Student's t *test for paired data* was used to test the significance of differences between mean values.[18]

Results

Group I: The hemodynamic findings in the control animals during the two periods of ischemia are shown in Table I. There was no significant difference between the first and second occlusions. There was also no significant change in the S-T map (Table II). There was excellent correlation between the distribution of radioactive microspheres and the degree of S-T segment elevation ($P < 0.01$). The endocardial/epicardial ratio remained unchanged in the nonischemic area but decreased in the ischemic area (Table II). There was also excellent correlation between the distribution of the triphenyl tetrazolium chloride stain and the S-T map. The mean infarct weight, as shown by the triphenyl tetrazolium chloride stain, was 14.5 ± 1.4 g/100 g left ventricular weight. In five of the six hearts the infarct was diffuse and solid. In the remaining heart the infarct mainly involved the inner half of the myocardium. Electron microscopic studies showed severe ischemic damage in the infarct center, with variable changes at the margin and no changes in the nonischemic myocardium.

Group II: The hemodynamic effects of left ventricular to aortic assistance instituted in this group just before the second occlusion are shown in Table I. The servomechanism allowed complete bypass, and no dogs died of air embolism. During the 5 hour period of occlusion, the servocontrol reliably adjusted the pump flow. After institution of assistance (Table I), there was a statistically significant reduction in the systolic left ventricular pressure (Fig. 2) and in the pressure-time index ($P < 0.005$).

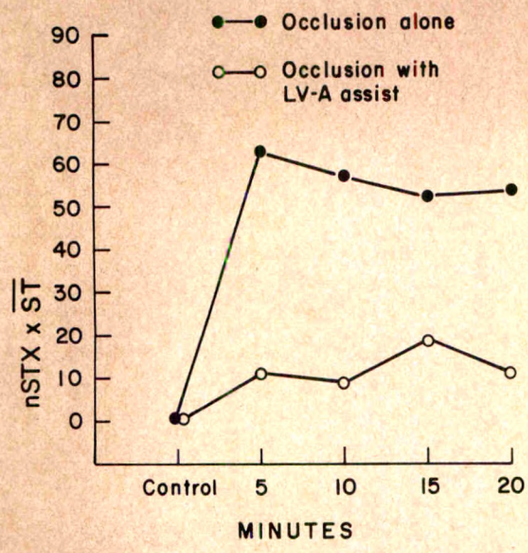

FIGURE 3. The effect of left ventricular to aortic (LV-A) assistance on infarct size as measured by S-T segment mapping in an experiment from Group II. During the second occlusion, the product of nST (number of sites with more than 2 mm S-T segment elevation) and $\overline{ST}$ (mean S-T segment elevation) is markedly reduced.

Left ventricular to aortic assistance resulted in a significant reduction in infarct size as measured with S-T segment mapping (Table II, Fig. 3). Discontinuing assistance for 5 minutes at 1 hour resulted in an elevation in S-T segments; the segments returned to previous levels after institution of assistance.

Injection of microspheres showed a reduction in flow in the area of the infarct (Table II), primarily in the subendocardial area. However, the endocardial/epicardial flow ratio in the ischemic area increased during the second occlusion with left ventricular to aortic assistance, whereas it decreased in our control group and in the group with left atrial to aortic assistance previously reported on (Table II, Fig. 4).

Infarct weight (Table II) was significantly less in this group than in the control group ($P < 0.05$), and the infarct itself tended to be more patchy and to lie mainly in the subendocardial area. Electron microscopic studies of multiple biopsy specimens also showed less striking and more variable ischemic changes in the area of the infarct in this group than in the control group.

Group III: In these seven dogs left ventricular to aortic assistance was begun after 20 minutes of ischemia. The effects of this assistance on hemodynamic variables are shown in Table I. As in Group II, there was a statistically significant reduction in infarct size as measured with the S-T map (Table II, Fig. 5). The distribution of radioactive microspheres was also similar to that in Group II. The endocardial/epicardial ratio increased 20 minutes after the onset of assistance as in Group II. The infarct was also less diffuse than in the control group.

Left atrial to aortic assistance: The reported effects of left atrial to aortic assistance on hemodynamics, infarct size and blood flow distribution are shown in Tables I and II.[12] The hemodynamic data were similar to those of the present groups except that left ventricular pressure remained at systemic levels in contrast to findings in our Groups II and III with left ventricular to aortic assistance (Fig. 2). In addition, the pressure-time index was significantly reduced but to a lesser degree than in Groups II and III. Infarct size was not significantly reduced with left atrial to aortic assistance (Table II). The endocardial/epicardial blood flow ratio in the ischemic area was reduced during the second occlusion, as in our control group, in contrast to the increased ratio in our groups with left ventricular to aortic assistance (Table II, Fig. 4).

Discussion

Effect on myocardial perfusion: Infarct size was measured with three techniques to avoid the limitations

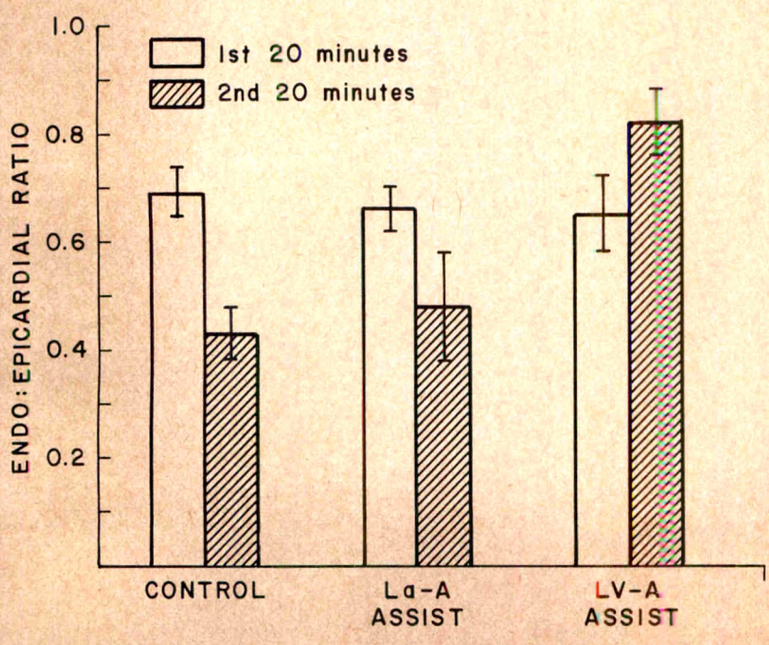

FIGURE 4. The endocardial (endo) to epicardial ratio of microsphere distribution in the ischemic area for the three experimental groups at the end of the first 20 minute period of ischemia. Both the control group and the group with left atrial to ventricular (La-A) assistance show a reduction in the endocardial to epicardial ratio while the left ventricular to aortic (LV-A) assist group shows a rise in this ratio.

of any one method. The method of S-T segment mapping, as described by Maroko et al.,[19] has received wide application, although its reliability has been questioned.[20] A cotton-tipped electrode was used in our study, rather than a grid as described by others,[11] to avoid displacement of the electrodes as left ventricular decompression reduces heart size. In all groups, the S-T segment map correlated well with the distribution of coronary blood flow as measured with radioactive microspheres and the triphenyl tetrazolium chloride stain.[17] Although some authors[21,22] have found a weak correlation between epicardial S-T segment elevation and myocardial blood flow, others[23] have found a good correlation between these variables. In our study there was excellent correlation ($P < 0.01$) between the degree of S-T elevation and the reduction of flow as indicated by the radioactive microsphere distribution. In the control group there was a reduction in the endocardial/epicardial ratio of microsphere distribution in the ischemic area between the first and second occlusions. This was also found in the previously reported study of left atrial to aortic assistance.[12] In contrast, left ventricular to aortic assistance resulted in an elevation of the endocardial/epicardial ratio in the normal area in Group II ($P < 0.05$) and in the ischemic area in Group III ($P < 0.05$, Fig. 4). In our control group and in the groups with left atrial to aortic assistance previously reported on, we believe that the first occlusion possibly left some residual subendocardial damage or edema that resulted in the reduced perfusion during the second occlusion. However, with left ventricular to aortic assistance, the reduction in left ventricular pressure resulted in improved subendocardial perfusion (Table I).

Effect on infarct size: The triphenyl tetrazolium chloride stain has been shown to delineate reliably an infarct of several hours' duration.[17] In this study the triphenyl tetrazolium chloride stain distribution was corroborated with electron microscopic studies that showed severe damage in the unstained area and minor changes or normal myocardium in the stained areas. There was also excellent correlation between the distribution of radioactive microspheres and the results of triphenyl tetrazolium chloride staining. Infarct weight, as measured with this stain, was significantly less ($P < 0.05$) in the groups with left ventricular assistance than in the control group or the animals with left atrial to aortic assistance (Table II).

The infarct produced in this study was a large one caused by occlusion of the proximal left anterior descending coronary artery rather than a diagonal branch of this artery. It has previously been shown[11] that only high degrees of bypass are effective in a large infarct model. This finding was confirmed in our previous study,[12] which showed that left atrial to aortic assistance reduced infarct size in a small infarct model but was less effective when the proximal left anterior descending coronary artery was occluded (Table II). In contrast, left ventricular to aortic assistance effectively reduced infarct size whether it was started immediately before (Group II) or 20 minutes after (Group III) occlusion.

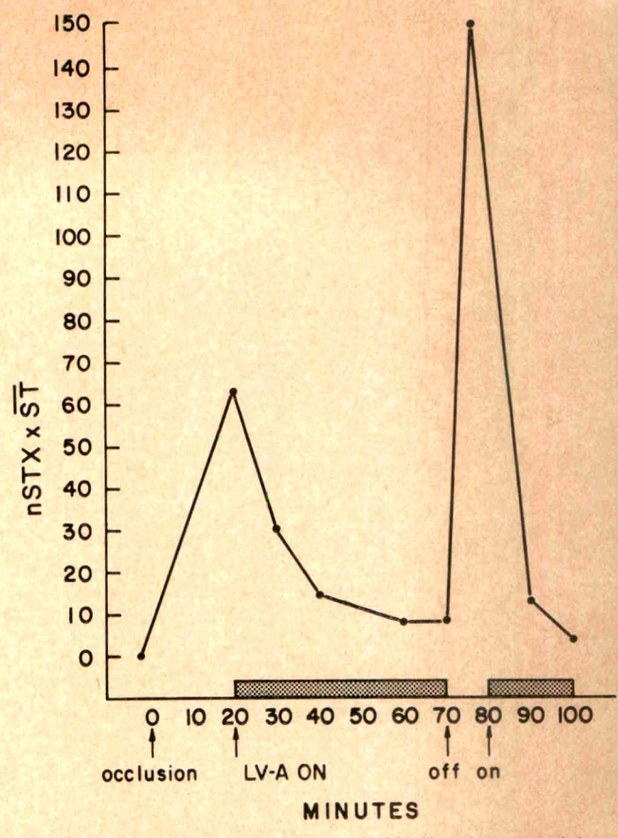

FIGURE 5. Effect of left ventricular to aortic (LV-A) assistance on infarct size from an experiment in Group III where assistance is instituted after 20 minutes of occlusion. Left ventricular to aortic assistance causes a reduction in the product of nST (number of sites with S-T segment elevation) and $\overline{ST}$ (mean S-T segment elevation). When left ventricular assistance is discontinued for 10 minutes, there is a marked elevation in this product, which is again reduced by reinstitution of left ventricular to aortic assistance.

Left ventricular to aortic assistance effectively reduced left ventricular pressure below systemic levels (Table I), whereas left atrial to aortic assistance even of high degree did not reduce left ventricular systolic pressure (Fig. 2).[12] It has been shown that the major determinant of myocardial oxygen consumption is pressure rather than volume work.[24] In our study, left ventricular to aortic assistance resulted in a far greater reduction in the pressure-time index (63 percent), than did left atrial to aortic assistance (15 percent) (Table I). It is therefore not surprising that left ventricular to aortic assistance was more effective in reducing infarct size.

Clinical applications: Cardiac assistance is now being applied clinically.[2] Left atrial to aortic assistance, used by Litwak et al.,[2] has been effective in salvaging life. The device used consists of a simple roller pump with silicone rubber cannulas, attached to the left atrium and the aorta, which can be obturated and left implanted after disconnection. We have reported[3] on our experience with this device in three patients; all three could be weaned from bypass only with cardiac

assistance and one of them is currently a 3 year survivor. A second device now being tested clinically consists of a pneumatically driven single-chambered pump with a polyurethane bladder, which pumps blood from the left ventricular apex to the abdominal or thoracic aorta.[6,7] This device can be either implanted in the abdomen[7] or placed extracorporeally on the chest.[6] Although the clinical results of the abdominal device for left ventricular assistance have been disappointing in terms of survival, this may be due to resorting to cardiac assistance too late in the patient's course. Clinical experience has demonstrated that cardiac recovery occurs, allowing disconnection from the assist device, but that multiorgan failure often ensues as a complication of the low output state that precedes institution of assistance.[7]

Our study suggests that there is an advantage in left ventricular to aortic assistance over left atrial to aortic assistance for salvage of ischemic myocardium. Using cannulas that have been developed for left ventricular apical insertion,[4,5] the servocontrolled roller pump offers a simple method for postoperative cardiac assistance.

Acknowledgment

The servomechanism was developed and built with the invaluable assistance of J. Briar. The technical assistance of H. Scott is gratefully acknowledged.

References

1. **DeBakey ME:** Left ventricular bypass pump for cardiac assistance: clinical experience. Am J Cardiol 27:3–11, 1971
2. **Litwak RS, Koffsky RM, Jurado RA, et al:** Use of left heart assist device after intracardiac surgery: technique and clinical experience. Ann Thorac Surg 21:191–202, 1976
3. **Laks H, Marco JD, Farmer TL, et al:** A servo controlled atrial-to-aortic assist device: experimental findings and clinical experience. Ann Thorac Surg 22:546–556, 1976
4. **McRea JC, Peters JL, Fukumasu H:** Blood access system developed for transapical left ventricular bypass (TALVB). Trans Am Soc Artif Intern Organs 23:309–313, 1977
5. **Laks H, Ott RA, Hahn JW, et al:** A servo controlled transapical left ventricular to aortic assist device with implantable cannulae. Trans Am Soc Artif Intern Organs 23:319–325, 1977
6. **Bernard WR, Poirier V, LaFarge CG, et al:** A new method for temporary left ventricular bypass. J Thorac Cardiovasc Surg 70: 880–895, 1975
7. **Norman JC:** Intracorporeal partial artificial hearts: initial results in ten patients. Artif Organs 1:41–52, 1977
8. **DeLaria GA, Johansen KH, Levine ID, et al:** Reduction in myocardial ischemia by left ventricular bypass after acute coronary artery occlusion. J Thorac Cardiovasc Surg 67:826–837, 1974
9. **Hughes DA, Igo SR, Daly BDT, et al:** Effects of an abdominal left ventricular assist device on myocardial oxygen supply/demand ratios in normally perfused and ischemic bovine myocardium. Ann Thorac Surg 19:301–308, 1975
10. **Miller DR:** Comparative effects of left atrial or left ventricular bypass on coronary sinus flow and oxygen usage in dogs. Ann Surg 179:830–835, 1974
11. **Pennock JL, Pierce WS, Waldhausen JA:** Quantitative evaluation of left ventricular bypass in reducing myocardial ischemia. Surgery 79:523–533, 1976
12. **Laks H, Ott RA, Standeven JW, et al:** The effect of left atrial-to-aortic assistance on infarct size. Circulation 56:Suppl II:II-38–II-43, 1977
13. **Pennock JL, Pierce WS, Prophet GA, et al:** Myocardial oxygen utilization during left heart bypass. Arch Surg 109:635–641, 1974
14. **Dennis C, Hall DP, Moreno JR, et al:** Reduction of the oxygen utilization of the heart by left heart bypass. Circ Res 10:298–305, 1962
15. **Salisbury PF, Bor N, Lewin RJ, et al:** Effects of partial and of total heart-lung bypass on the heart. J Appl Physiol 14:458–463, 1959
16. **Jacobs G, Hinglais J:** Left heart bypass and myocardial oxygen uptake: experimental data for the non failing heart, chap 9. In, Mechanical Assistance of the Circulation, Assistierte Zirkulation, Colloquium in Bad Nevenahr, June 15–17, 1967 (Loogen F, Bostroem B, Gleichmann U and Kreuzer H, ed). Stuttgart, New York, Intercontinental Medical Book, 1967, p 96–102
17. **Lie JT, Pairolero PC, Holley KE, et al:** Macroscopic enzyme-mapping verification of large, homogenous, experimental myocardial infarcts of predictable size and location in dogs. J Thorac Cardiovasc Surg 69:599–605, 1975
18. **Goldstein H:** Biostatistics. New York, Macmillan, 1964, p 59
19. **Maroko PR, Libby P, Covell JW, et al:** Precordial S-T segment mapping: an atraumatic method for assessing alterations in the extent of myocardial ischemic injury. The effects of pharmacologic and hemodynamic interventions. Am J Cardiol 29:223–230, 1972
20. **Holland RP, Brooks H:** TQ-ST segment mapping: critical review and analysis of current concepts. Am J Cardiol 40:110–129, 1977
21. **Smith HJ, Singh BN, Norris RM, et al:** Changes in myocardial blood flow and S-T segment elevation following coronary artery occlusion in dogs. Circ Res 36:697–705, 1975
22. **Irvin RG, Cobb FR:** Relationship between epicardial S-T segment elevation, regional myocardial blood flow and extent of myocardial infarction in awake dogs. Circulation 55:825–832, 1977
23. **Wegria R, Segers M, Keating RP, et al:** Relationship between the reduction in coronary flow and the appearance of electrocardiographic changes. Am Heart J 38:90–96, 1949
24. **Sarnoff SJ, Braunwald E, Welch GH Jr, et al:** Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index. Am J Physiol 192:148–156, 1958

Early Quantification of Experimental Myocardial Infarction With Technetium-99m Glucoheptonate: Scintigraphic and Anatomic Studies

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Recent advances in understanding of the pathophysiology of myocardial necrosis indicate the need for a noninvasive method that will allow detection and quantification of infarcts in the first few hours after the onset of infarction. Myocardial infarct scintigraphy using technetium-99m glucoheptonate is capable of detecting infarction in dogs and man within 4 to 6 hours of onset. Studies were performed in 45 dogs with acute myocardial infarction: 28 with an anterior infarct, 5 with an inferior infarct, 6 with an anterior infarct studied after infusion of mannitol and 6 with ligation of the left anterior descending coronary artery and reperfusion of the ischemic area. The dogs were given 20 mCi of technetium-99m glucoheptonate 1 hour after coronary occlusion, subjected to imaging 5 to 9 hours later and then killed. The experiments revealed that (1) scintigraphic infarct size correlated with infarct weight for anterior ($r = 0.85$) and inferior ($r = 0.88$) infarcts; (2) technetium-99m glucoheptonate also concentrated in a rim of myocardium around the infarct that probably represented the ischemic zone; and (3) technetium-99m glucoheptonate uptake by infarcted myocardium could be greatly increased with mannitol and reperfusion.

Direct noninvasive visualization of experimental myocardial infarcts using an infarct-avid radiopharmaceutical agent was first accomplished by Carr et al.[2] in 1963 with mercury-203 chlormerodrin. Myocardial infarct scintigraphy did not become practical and acceptable clinically until Holman et al.[2] introduced the use of technetium-99m tetracycline, ushering in a new era in the diagnosis and quantification of acute myocardial infarction. They demonstrated that technetium-99m tetracycline accumulates preferentially in acute myocardial infarcts, permitting external detection 24 to 48 hours after the onset of infarction. Bonte and his co-workers[3] later reported on the value of technetium-99m pyrophosphate as an imaging agent. Images of sufficient quality to allow quantification of infarct size in dogs[4] and man[5] were shown to be obtained reliably in infarcts at least 24 hours old.

Concurrently, other investigators, notably Maroko et al.[6] and Jennings et al.[7] demonstrated that experimental ischemic myocardial necrosis evolves gradually over a number of hours so that a variety of therapeutic interventions can potentially stop or even reverse the process. Best estimates indicate that this critical period from onset to completion of myocardial necrosis may last as long as 6 to 18 hours after coronary ligation in the dog.[7–9] Thus, ischemia-damaged portions of myocardium that would otherwise undergo necrosis are potentially salvageable during the initial hours after coronary occlusion. Although this revolutionary concept has not been confirmed in man, the preliminary evidence is favorable.[10,11] Hence, there exists the need for a noninvasive method of detecting and estimating infarct size in the first few hours after the onset

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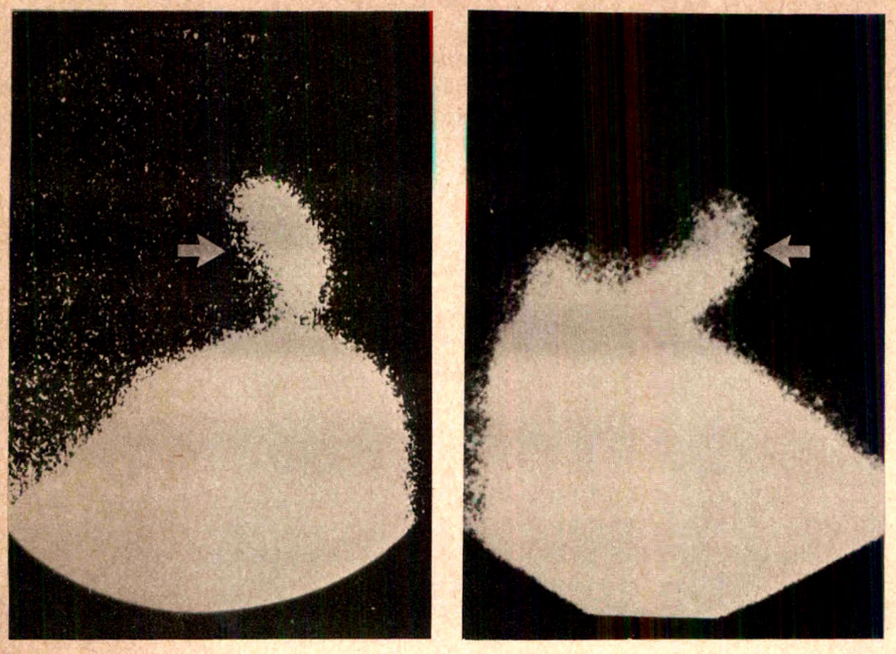

FIGURE 1. Technetium-99m glucoheptonate scintigrams in two dogs with an acute experimental myocardial infarct. **Left,** right anterior oblique view of a 7 hour old anterior infarct **(arrow). Right,** left anterior oblique view of a 5 hour old inferior infarct **(arrow).** In both scintigrams, the large white area under the infarct represents uptake in the liver.

of infarction. Our group has been exploring one such method: myocardial infarct scintigraphy utilizing technetium-99m glucoheptonate. The latter radiopharmaceutical agent is capable of detecting and localizing acute myocardial infarcts in dogs[12–14] and man[15,16] within 4 to 6 hours of onset of infarction. This communication reports on basic studies on myocardial localization of technetium-99m glucoheptonate and on quantification of myocardial infarcts utilizing this agent.

Material and Methods

Experimental Model

Mongrel dogs weighing 15 to 27 kg were anesthetized with sodium-pentobarbital (25 mg/kg body weight). In most of the animals, the heart was exposed through a thoracotomy in the sixth left intercostal space, the pericardium was opened and a pericardial cradle constructed. The left anterior descending coronary artery was ligated distal to the origin of the first diagonal branch, usually 2 to 3 cm from its origin, or the left circumflex coronary artery was ligated proximal to the origin of the obtuse marginal branch. In several of the later studies, either the left anterior descending or left circumflex artery was occluded by embolization of a metal bead of appropriate size through a Judkins L-4 coronary arterial catheter. This was done to avoid uptake of technetium-99m glucoheptonate in the surgical wound and to prevent the interference caused by overlap of this uptake with that in the myocardial infarct. In a separate subset of dogs, reversible coronary occlusion was produced by means of a modified Fogarty balloon catheter attached to an 8 mm Dacron® cuff. The balloon was inflated externally around the artery, producing the occlusion.

The 45 dogs with acute myocardial infarction that were studied were grouped as follows:

Unmodified infarct group (33 dogs): Twenty-eight dogs underwent occlusion of the left anterior descending coronary artery and five occlusion of the left circumflex coronary artery, resulting in an anterior and diaphragmatic infarct, respectively. No dog in this group received any treatment except for occasional intravenous administration of lidocaine to prevent ventricular arrhythmias.

Mannitol group (six dogs): Anterior wall myocardial infarction was induced in six dogs by occlusion of the left anterior descending coronary artery. Fifteen minutes after occlusion, 200 cc of 25 percent mannitol was administered intravenously over a period of 50 minutes. Additional doses of 50 cc of 25 percent mannitol were given every 3 hours until the dogs were killed 8 to 10 hours after infarction.

Reflow group (six dogs): In six dogs, the left anterior descending coronary artery was reversibly occluded by inflation of the modified Fogarty catheter. The effectiveness of the occlusion was confirmed with selective coronary arteriography and the thoracotomy closed. Occlusion was maintained for 30 minutes to 3 hours. Reperfusion of the previously ischemic region was effected by deflation of the balloon and maintained until the dogs were killed 8 hours after the initial coronary occlusion.

Imaging Studies

Dogs in all groups were given an intravenous injection of 15 to 20 mCi of technetium-99m glucoheptonate 1 hour after coronary occlusion. Imaging was performed with a Picker Dyna Camera 2C. Scintigrams were obtained in four projections (left lateral, left anterior oblique, anterior and right anterior oblique) 5 to 9 hours after injection (6 to 10 hours after infarction). All studies were recorded on videotape for permanent storage and on Polaroid® film.

Scintigraphic infarct size was determined using planimetry of the area of abnormal uptake in the region of the myocardium. For anterior wall infarcts (produced with occlusion of the left anterior descending coronary artery), the right anterior oblique projection was used because the cross-sectional area of the infarct tended to be best defined in this view (Fig. 1, left). For inferior wall infarcts (produced with occlusion of the left circumflex coronary artery), planimetry was performed

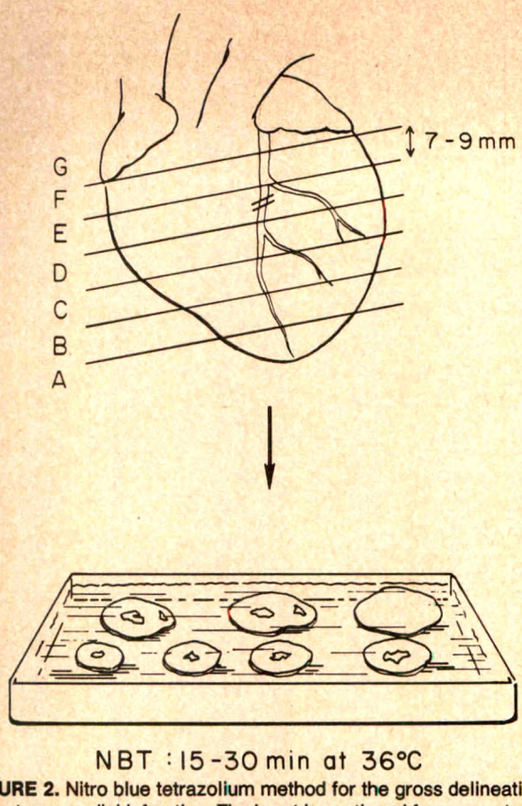

FIGURE 2. Nitro blue tetrazolium method for the gross delineation of recent myocardial infarction. The heart is sectioned from apex to base in a plane parallel to the atrioventricular groove. The ventricular slices are then incubated for 15 to 30 minutes at 36° C in a solution of nitro blue tetrazolium in Sorensen's buffer.[17]

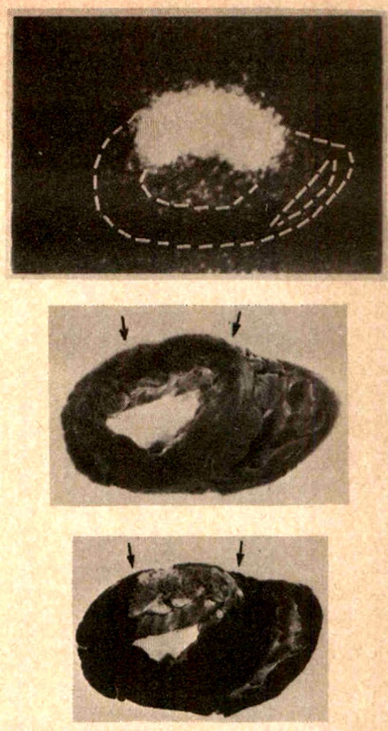

FIGURE 3. Postmortem studies performed on cardiac slices. **Top,** scintigram of isolated ventricular slice shown in the **center panel.** Intense concentration of radioactivity corresponds to the location of the infarct as shown in the **bottom panel.** The outline of the unlabeled myocardium is indicated by the **dashed lines. Center,** appearance of cardiac slice before nitro blue tetrazolium incubation. Barely perceptible area of discoloration is seen in the left anterior wall **(arrows). Bottom,** same cardiac slice shown in center panel after incubation in nitro blue tetrazolium solution. The transmural infarct is now clearly delineated as a light area **(arrows).** Normal myocardium stains dark blue **(black** in photograph).

on the left anterior oblique projection because the cross-sectional area of these infarcts tended to be greatest in this projection (Fig. 1, right). Polaroid® photographs of myocardial scintigrams were projected to life size with an opaque projector and their outline traced on a sheet of white paper, using a standard projector-to-paper distance. This distance was determined by obtaining a Polaroid photograph of two cobalt-57 markers positioned 8 inches (20 cm) apart, 5 cm in front of the gamma camera detector. This photograph was then projected at a distance that produced an image in which the radioactive markers were 8 inches apart. The lower border of inferior wall infarcts was frequently contiguous with the silhouette of the liver in technetium-99m glucoheptonate scintigrams (Fig. 1, right). The inferior border of the infarct was determined by extrapolating the edge of the liver under the infarct from its visible borders at both sides of the infarct. This line and its continuation around the visible lateral and superior borders of the area of technetium-99m glucoheptonate uptake over the heart delineated the boundaries of the myocardial infarct for the purposes of planimetry.

Postmortem Studies

After completion of the imaging studies, the dogs were killed with an overdose of pentobarbital. The following studies were then carried out:

Isolated heart and ventricular slices: Scintigrams of the isolated heart were obtained immediately upon removal, in an approximately anterior position. The heart was then sectioned from apex to base every 7 to 9 mm, in a plane parallel to the atrioventricular groove (Fig. 2), and each slice was imaged (Fig. 3, top) and weighed.

Histochemical and histological procedures: All infarcts in this study were between 6 and 10 hours old when the dogs were killed. Infarcts of such recent onset are barely visible on gross examination of the pathologic specimen and their borders are not clearly defined (Fig. 3, center). To circumvent this difficulty, nitro blue tetrazolium staining for the gross demonstration of myocardial dehydrogenases was performed on the ventricular slices (Fig. 2). This technique, as described by Nachlas and Schnitka,[17] provides an accurate gross delineation of recent myocardial infarcts. Normal myocardium that is stained blue is clearly differentiated from the unstained infarcted tissue (Fig. 3, bottom).

Blocks of tissue from the infarct and adjacent normal myocardium were fixed in 10 percent buffered formalin, embedded in paraffin and stained with hematoxylin-eosin, periodic acid-Schiff stain with and without diastase digestion and the Alizarin red method for calcium.

Calculation of infarct weight: Color transparencies of the ventricular slices were obtained after nitro blue tetrazolium incubation. These photographs, which showed a clear delineation of the infarcted areas (Fig. 3, bottom), were projected and traced, thus providing a map of the infarct in each

slice (Fig. 4). The area occupied by the infarct on both cut surfaces of each slice was determined with planimetry and averaged. The weight of infarcted tissue in each slice was calculated by multiplying the average area of the infarct (as percent of the total area of the slice) by the weight of the slice. Total infarct weight was calculated by summing the weight of the infarct in each slice (Fig. 4). To assess the reproducibility of the method, repeat measurements were obtained and the values were consistently within 3 percent of each other.

Myocardial levels of radioactivity: The distribution of technetium-99m glucoheptonate uptake at the tissue level was determined by scintillation well counting of small myocardial samples (20 to 200 mg each). Transmural infarcts were divided into three zones: subendocardial, mid zonal and epicardial. Several samples from each of these zones were obtained, weighed and counted in a scintillation well counter. An average number of 15 samples per infarct were counted. In addition, five consecutive narrow bands (approximately 10 by 1 by 1 mm) immediately adjacent to the lateral and septal borders of the infarct defined with nitro blue tetrazolium staining were dissected and counted. These small myocardial samples were obtained from positive stained areas immediately adjacent to the infarct. This study of the uptake of technetium-99m glucoheptonate by the border zone was performed in 13 dogs with a transmural infarct from the control (unmodified infarct) group. Myocardial levels of technetium-99m glucoheptonate uptake were expressed as infarct/normal myocardium ratios. Normal myocardium was obtained from the uninvolved areas of the left ventricular wall, remote from the region of the infarct.

Results

Scintigraphic demonstration and localization of experimental myocardial infarcts: All dogs showed unequivocal uptake of technetium-99m glucoheptonate in the infarct and border definition sufficient for reproducible planimetric measurement at the time of imaging (6 to 9 hours after injection, 7 to 10 hours after infarction). The five inferior wall infarcts resulting from occlusion of the left circumflex artery were readily distinguishable from the anterior wall infarcts produced by occlusion of the left anterior descending coronary artery. The left and right panels of Figure 1 show the typical appearance of an anterior and inferior infarct, respectively. The cup-shaped area of uptake seen in the inferior infarct in the left anterior oblique view was clearly visible in all cases in spite of continuity with the activity in the liver. In some cases, a portion of the infarct border overlapped slightly with the liver and the border had to be estimated. No differences were noted between the scintigrams of the control group and the group receiving mannitol. However, the three dogs with reperfusion in which transmural infarcts developed showed substantially more uptake in the infarct area than the other animals.

Quantification of acute experimental myocardial infarction: *Anterior wall infarcts:* Figure 5 illustrates a strongly positive correlation between scintigraphic infarct size in the right anterior oblique view and infarct weight determined at autopsy for the animals with an anterior wall infarct (correlation coefficient [r] = 0.85). In these dogs infarct weight varied over a wide range (from 0.5 to 28 g) in spite of a relatively uniform level

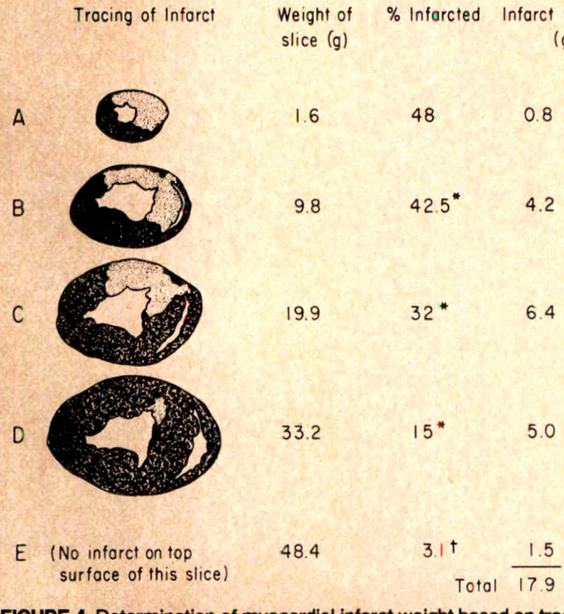

FIGURE 4. Determination of myocardial infarct weight based on tracings of infarcts outlined with the nitro blue tetrazolium method. *These values were obtained by averaging the infarcted areas present in both surfaces of each slice. † There is no visible infarct in the basal surface of slice E although its apical surface contains an infarct of approximately equal area ot that present in the basal surface of D. This area is halved and multiplied by the weight of slice E to obtain the weight of the infarct in slice E.

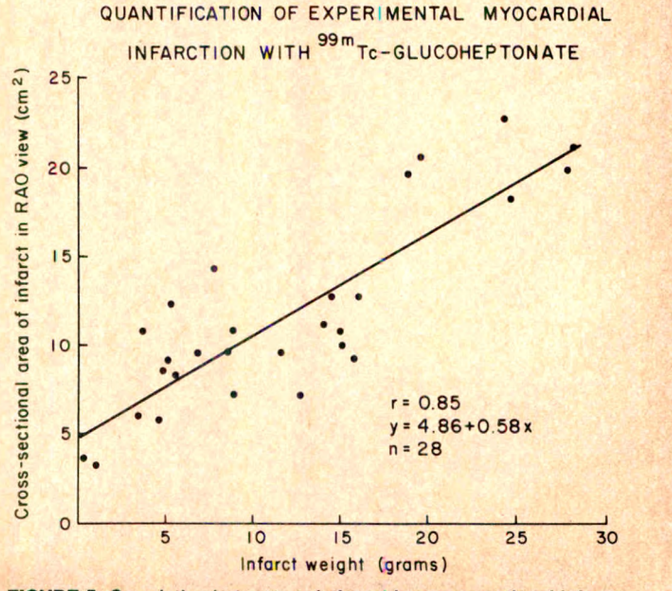

FIGURE 5. Correlation between scintigraphic cross-sectional infarct area in the right anterior oblique (RAO) view and infarct weight determined at autopsy in 28 dogs with an acute anterior myocardial infarct. n = number of dogs.

of occlusion of the left anterior descending coronary artery just beyond the major diagonal branch or approximately 2 cm from its origin.

Inferior wall infarcts: Figure 6 illustrates a similar positive correlation between the cross-sectional area of technetium-99m glucoheptonate uptake in the left anterior oblique projection and actual infarct weight in five dogs with an inferior wall infarct (r = 0.88). This excellent correlation was obtained even though uptake over the infarct area was contiguous with the activity within the liver.

Technetium-99m glucoheptonate concentration within experimental myocardial infarction: *Unmodified infarct group:* Scintillation well counting of multiple small samples of tissue from the infarct, immediately adjacent regions and remote normal myocardium demonstrated that technetium-99m glucoheptonate is highly concentrated in the infarct. The peripheral zone of the infarct was compared with the center. Relative uptake was expressed as infarct/normal myocardium ratio. A gradient of uptake was a constant finding in both anterior and inferior wall infarction. In the unmodified infarct group, the average infarct/normal myocardium ratio ranged from 21:1 at the periphery to 5.5:1 at the center. However, the so-called doughnut sign, the presence of a relatively cold area in the center of the infarct, was seen only occasionally in the myocardial scintigrams.

Mannitol group: The tissue concentrations of technetium-99m glucoheptonate were measured in six dogs with an acute anterior myocardial infarct that received intravenous infusions of 25 percent mannitol. Figure 7 shows that mannitol provoked a statistically significant twofold increase in uptake within the infarct. This increased uptake was consistent throughout the endocardial, mid and epicardial thirds of transmural infarcts.

Reflow group: In three of the six dogs that underwent occlusion of the left anterior descending coronary artery, focally hemorrhagic transmural myocardial infarcts developed, although perfusion was reestablished 30 minutes to 3 hours after occlusion. In these three dogs, there was a fourfold increase in tissue levels of technetium-99m glucoheptonate in the endocardial portion of the infarcts. Similar although less marked elevation in myocardial uptake was observed in the mid and epicardial portions (Fig. 7). Two other dogs that underwent temporary occlusion of the left anterior descending coronary artery had minute subendocardial infarcts (0.5 and 1.1 g, respectively). The remaining dog had no infarct and demonstrated no increased uptake of technetium-99m over the myocardium as documented with myocardial imaging and scintillation well counting.

Technetium-99m glucoheptonate uptake by myocardium adjacent to a transmural infarct: Technetium-99m glucoheptonate uptake was also documented in myocardial samples obtained from the area immediately adjacent to the infarct but shown to be normal with both nitro blue tetrazolium staining and histologic examination. These samples of "normal" myocardium were obtained in 1 mm increments from the lateral and septal borders of the infarct (Fig. 8). The rim of "normal" myocardium that concentrates technetium-99m glucoheptonate measured approximately 3 to 4 mm. The concentration decreased rapidly with distance and reached normal levels approximately 5 mm from the edge of the infarct (Fig. 8).

Discussion

The recent interest in attempts to preserve potentially reversible areas of ischemic myocardium during the first hours after coronary occlusion has awakened new interest in methods designed to quantify myocardial infarct size. Those currently available, creatine kinase estimation of infarct size and precordial S-T segment mapping, appear to be limited in their clinical application.[18,19] There still exists a need for a reliable method to measure infarct size in man. Ideally, this method should: (1) detect and localize acute myocardial infarction within a few hours of onset; (2) measure the actual size of the infarct or at least provide a reasonable index of infarct size; and (3) be able to detect and quantify (a) infarct extension, and (b) limitation of ultimate infarct size resulting from interventions designed to preserve ischemic myocardium.

Our data show that imaging with technetium-99m glucoheptonate fulfills the first two requirements in acute experimental canine myocardial infarction. The third point, namely, the capability of the method to demonstrate extension or reduction of ischemic injury, is now under investigation.

Technetium-99m glucoheptonate permits the detection, localization and quantification of an acute experimental myocardial infarct within a few hours of the

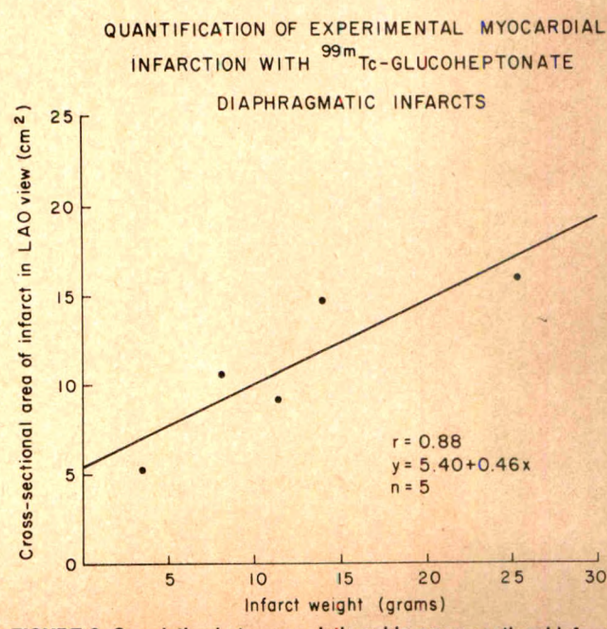

FIGURE 6. Correlation between scintigraphic cross-sectional infarct area in the left anterior oblique view and infarct weight determined at autopsy in five dogs with an acute diaphragmatic myocardial infarct.

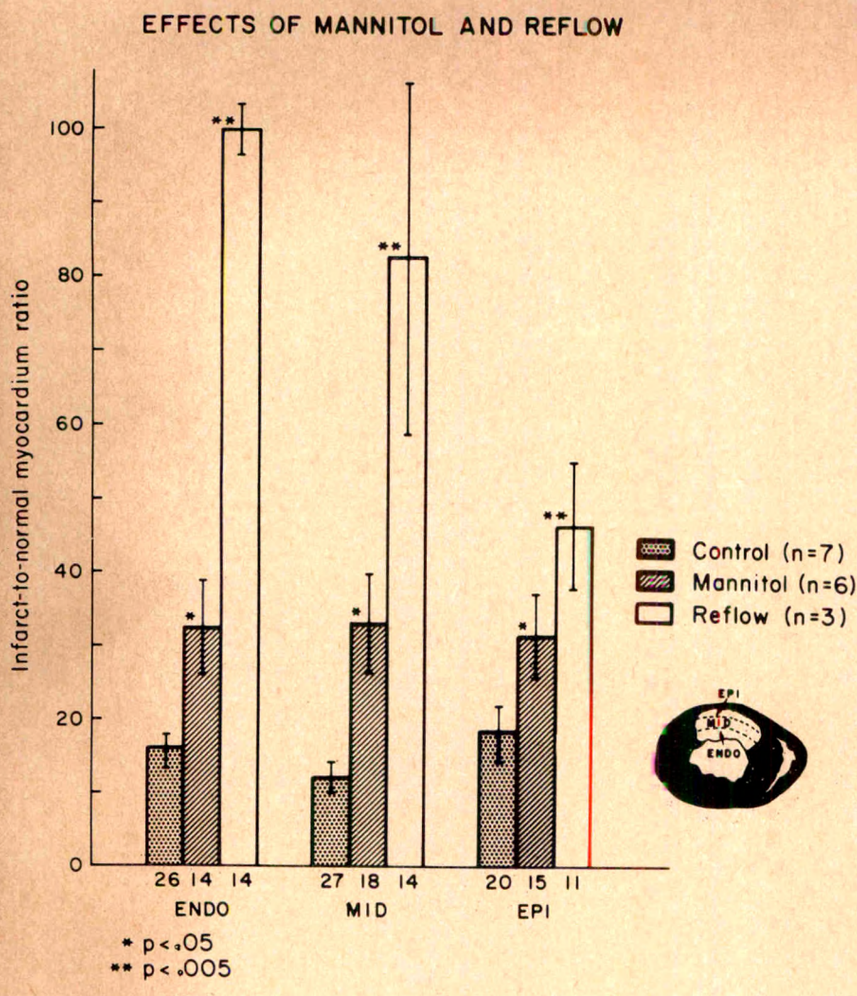

FIGURE 7. Effects of mannitol and reflow on the uptake of technetium-99m glucoheptonate by infarcted myocardium. ENDO = endocardial; EPI = epicardial; MID = mid myocardial; n = number of dogs; p = probability.

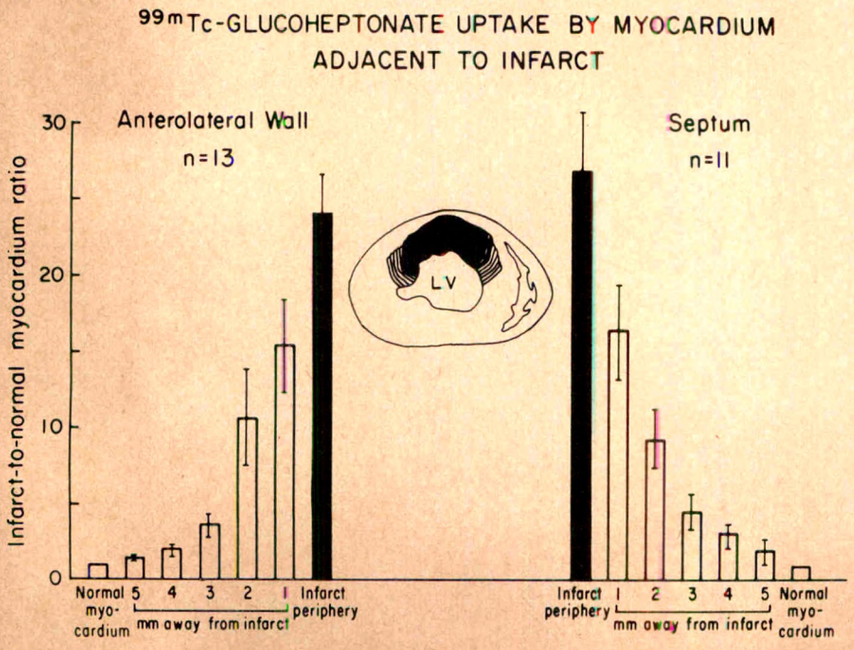

FIGURE 8. Uptake of technetium-99m glucoheptonate by the myocardium adjacent to myocardial infarcts. The cardiac slice in the center of the figure shows an anterior infarct **(black)** and adjacent myocardium from which samples were obtained to determine technetium-99m glucoheptonate concentrations (expressed as infarct/normal myocardium ratio). LV = left ventricular cavity; n = number of dogs.

onset of infarction. We have previously shown[14] that canine infarcts of both the anterior and inferior walls can be consistently demonstrated by imaging with technetium-99m glucoheptonate as early as 4 hours after coronary occlusion. Other infarct-seeking radiopharmaceutical agents used for this purpose, such as technetium-99m pyrophosphate and technetium-99m tetracycline, are not reliable for imaging acute infarcts until a minimum of 24 hours after onset.[2,3]

Reliability in estimating infarct size: Technetium-99m glucoheptonate appears to be a very sensitive detector of small infarcts, at least in dogs. The two smallest infarcts detected with technetium-99m weighed 0.5 and 1.3 g, respectively (Fig. 5). We found a direct relation between the cross-sectional area of increased uptake in the scintigram and infarct weight at autopsy. By measuring the cross-sectional area of uptake with planimetry, it has been possible to obtain correlation coefficients of 0.85 and 0.88 for anterior and inferior infarcts, respectively. After completion of this study a subset of dogs with myocardial infarction were evaluated with a computer technique designed to improve and automate the delineation of scintigraphic infarct borders. This method, developed by Dr. Patrick Cahill of our group, uses an operator-independent edge-detection algorithm based on the nearest neighbor principle.[20] With this technique, correlation coefficients for anterior wall infarcts increased to 0.93[20] from the 0.85 achieved with the visual method. Thus, technetium-99m glucoheptonate imaging consistently detects early canine infarcts and provides a reliable estimate of their size by 6 hours after coronary occlusion. This property is not shared by any other infarct-labeling radiopharmaceutical agents currently available.

Distribution of myocardial tissue concentration: The greatest concentration of technetium-99m glucoheptonate is consistently at the periphery of the infarct, and from there its concentration decreases gradually, reaching a minimum in the center of the infarct. Such a distribution is very similar to that described for technetium-99m pyrophosphate[21,22] and is presumably due to the dependence of uptake on blood flow. In spite of this consistent gradient at the tissue level in the dogs given technetium-99m glucoheptonate, examination of the corresponding myocardial scintigrams showed only an occasional doughnut-shaped area of abnormal uptake.

Effect of mannitol and reperfusion: Of greatest interest is the potential ability of certain interventions to modify the tissue concentration ratio of technetium-99m glucoheptonate. The infusion of hyperosmotic mannitol solution shortly after coronary ligation resulted in approximately twice the myocardial uptake of technetium-99m glucoheptonate within the infarct compared with normal myocardium at the time of imaging. This suggests that it may be possible to increase infarct/background ratios and thereby improve image quality with pharmacologic means. Reperfusion of the infarcted myocardium after 30 minutes to 3 hours of coronary occlusion resulted in even greater relative uptake in the infarct; for example, infarct/normal myocardium ratios averaged 100:1 in the subendocardial third of transmural infarcts (Fig. 7).

Area of increased uptake adjacent to the infarct (border zone): Another finding of potential clinical significance that has been consistently documented in this study is the presence of technetium-99m glucoheptonate in myocardium immediately adjacent to the infarct. It concentrates in a narrow rim of grossly and histologically normal myocardium that also maintains the capability to reduce nitro blue tetrazolium; that is, it contains intact mitochondrial dehydrogenases. This area of increased uptake may represent the ischemic or "border" zone of the infarct. In addition to its uptake by dead or dying cells, it appears that technetium-99m glucoheptonate may accumulate in reversibly injured myocardium. If so, the labeling of some damaged myocardium by technetium-99m glucoheptonate is possibly transient and reversible and might be parallel to the fate of the ischemic zone. This would be an exciting prospect for the study of the dynamics of ischemic myocardium and for the evaluation of the effects of therapeutic interventions on infarct growth. However, we have not yet excluded two alternative explanations: (1) that this uptake represents some form of passive diffusion or leakage of the tracer from the immediately adjacent infarct, and (2) that nitro blue tetrazolium might have diffused from the normal myocardium into the adjacent infarct. This latter possibility is unlikely because nitro blue tetrazolium forms an insoluble formazan precipitate over the surface of the myocardium. Furthermore, electron microscopic studies recently performed in our laboratory indicate that evolving myocardial infarcts are surrounded by an ischemic border zone and that this border zone, composed of myofibers showing reversible ischemic damage, stains positive with nitro blue tetrazolium. In this sense, the nitro blue tetrazolium method underestimates the magnitude of ischemic injury because it fails to identify the jeopardized myocardium present around an evolving infarct.[23]

Clinical implications: From the data here presented and the definition of the injection and imaging schedule in dogs previously reported,[14] it is apparent that technetium-99m glucoheptonate has great potential for the early quantification of myocardial infarction. As opposed to other infarct-labeling radiopharmaceutical agents that have been tried or are currently in use for the diagnosis of myocardial infarction in man, technetium-99m glucoheptonate has the advantage of providing useful information within the first few hours after the onset of an acute myocardial infarction.

Such early information is important for at least two reasons. Accurate estimation of infarct size shortly after admission may prove helpful in management of the patient, particularly in the early institution of therapeutic measures before clinical evidence of failure or shock appears. In addition, during this crucial early period the extent of ischemic injury and ultimate amount of myocardial necrosis is being decided at the tissue level.[6–8] Myocardial imaging with technetium-99m glucoheptonate may provide an index of ischemic damage shortly after admission but before therapeutic

intervention that can be compared with later postintervention determinations of infarct size. It may thus be possible to evaluate the effects of intervention in the individual patient in an objective and noninvasive manner.

In spite of these very encouraging animal studies the final determination of the value of technetium-99m glucoheptonate will have to be made in patients. We believe that technetium-99m glucoheptonate deserves a full scale clinical trial to determine its ultimate role in the detection, localization and sizing of early myocardial infarction in patients and its potential value for the noninvasive evaluation of interventions designed to protect ischemic myocardium.

References

1. **Carr EA, Beierwaltes WH, Patno ME, et al:** The detection of experimental myocardial infarcts by photoscanning. Am Heart J 64:650–660, 1962
2. **Holman BL, Lesch M, Zweiman FG, et al:** Detection and sizing of acute myocardial infarcts with ^{99m}Tc (Sn) tetracycline. N Engl J Med 291:159–163, 1974
3. **Bonte FJ, Parkey RW, Graham KD, et al:** A new method for radionuclide imaging of myocardial infarcts. Radiology 110:473–474, 1974
4. **Stokely EM, Buja LM, Lewis SE, et al:** Measurement of acute myocardial infarcts in dogs with ^{99m}Tc-stannous pyrophosphate scintigrams. J Nucl Med 17:1–5, 1976
5. **Willerson JT, Parkey RW, Buja LM, et al:** Sizing acute myocardial infarction utilizing technetium stannous pyrophosphate myocardial scintigrams in dogs and man (abstr). Circulation 52:Suppl II:II-108, 1975
6. **Maroko PR, Kjekshus JK, Sobel BE, et al:** Factors influencing infarct size following experimental coronary artery occlusions. Circulation 43:67–82, 1971
7. **Jennings RB, Reimer KA:** Salvage of ishemic myocardium. Mod Concepts Cardiovasc Dis 43:125–128, 1974
8. **Reimer KA, Lowe JE, Rasmussen MM, et al:** The wavefront phenomenon of ischemic cell death. I. Myocardial infarct size vs duration of coronary occlusion in dogs. Circulation 56:786–794, 1977
9. **Braunwald E:** Protection of the ischemic myocardium: introductory remarks. Circulation 53:Suppl I:I-1–I-2, 1976
10. **Epstein SE, Borer JS, Kent KM, et al:** Protection of ischemic myocardium by nitroglycerin: experimental and clinical results. Circulation 53:Suppl I:I-191–I-197, 1976
11. **Russell RO Jr, Rogers WJ, Mantle JA, et al:** Glucose-insulin-potassium, free fatty acids and acute myocardial infarction in man. Circulation 53:Suppl I:I-207–I-209, 1976
12. **Rossman DJ, Siegel ME, Friedman BH, et al:** Accumulation of ^{99m}Tc-glucoheptonate in acutely infarcted myocardium (abstr). J Nucl Med 15:529, 1974
13. **Fink/Bennett D, Dworkin HJ, Lee YH:** Myocardial imaging of the acute infarct. Radiology113:449–450, 1974
14. **Jacobstein JG, Alonso DR, Roberts AJ, et al:** Early diagnosis of myocardial infarction in the dog with Technetium-99m glucoheptonate. J Nucl Med 18:413–418, 1977
15. **Rossman DJ, Rouleau J, Strauss HW, et al:** Detection and size estimation of acute myocardial infarction using ^{99m}Tc-glucoheptonate. J Nucl Med 16:980–985, 1975
16. **Combes JR, Jacobstein JG, Post MR, et al:** ^{99m}Tc-glucoheptonate imaging for the early diagnosis of acute myocardial infarction (abstr). Am J Cardiol 39:315, 1977
17. **Nachlas MM, Schnitka TK:** Macroscopic identification of early myocardial infarcts by alterations in dehydrogenase activity. Am J Pathol 42:379–405, 1963
18. **Roe CR, Starmer CF:** A sensitivity analysis of enzymatic estimation of infarct size. Circulation 52:1–5, 1975
19. **Heng MK, Sing BN, Norris RM, et al:** Relationship between epicardial ST-segment elevation and myocardial ischemic damage after experimental coronary artery occlusion in dogs. J Clin Invest 58:1317–1326, 1976
20. **Cahill PT, Ho SL, Jacobstein JG, et al:** Evaluation of edge detection algorithms for the delineation of myocardial infarcts with ^{99m}Tc-glucoheptonate. In, Proceedings of Seventh Symposium on Sharing of Computer Programs and Technology in Nuclear Medicine, Computer-Assisted Data Processing. Atlanta, Georgia, Society of Nuclear Medicine, January 1977, p 150–157
21. **Buja LM, Parkey RW, Dees JH, et al:** Morphologic correlates of technetium-99m stannous pyrophosphate imaging of acute myocardial infarcts in dogs. Circulation 52:596–607, 1975
22. **Buja LM, Parkey RW, Stokeley EM, et al:** Pathophysiology of technetium-99m stannous pyrophosphate and thallium-201 scintigraphy of acute myocardial infarcts in dogs. J Clin Invest 57: 1508–1522, 1976
23. **Gottlieb GJ, Alonso DR:** Morphologic characterization of the ischemic zone surrounding myocardial infarcts (abstr). Fed Proc 37:496, 1978

Echocardiographic Features of Congenital Mitral Stenosis

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To determine the echocardiographic features of congenital mitral stenosis, echocardiograms were obtained in 2 children with isolated mitral stenosis and 28 with mitral stenosis in association with other congenital heart defects. The diagnosis was confirmed at cardiac catheterization in all 30 patients and also at operation or autopsy in 12. The pattern of mitral valve motion was assessed qualitatively, and the amplitude of excursion of the anterior leaflet and the rate of early diastolic closure (E-F slope) were measured. The values were compared with those from 145 normal children, 22 children with isolated ventricular septal defect and 16 children with isolated coarctation of the aorta.

In patients with congenital mitral stenosis, the echocardiographic findings included diastolic anterior motion of the posterior leaflet of the mitral valve, absence of the *A* wave and reduction of the E-F slope. Diastolic vibration of the mitral leaflets occurred in 21 of the 30 patients with mitral stenosis and in 8 of the 145 normal children, but in none of the patients with coartation of the aorta. From the mitral valve echogram, it was not possible to determine whether the site of the inflow obstruction was the leaflets themselves, the chordae tendineae, the papillary muscles or a supravalve membrane.

Patients with severe stenosis tended to have a greater decrease in E-F slope and exhibited abnormal motion of the posterior mitral leaflet more frequently than patients with mild or only moderately severe mitral stenosis. However, the mitral valve echogram was more useful in detecting the presence of mitral stenosis, even in the presence of other cardiac malformations, than in determining the precise anatomy of the mitral valve lesion or estimating its severity.

Mitral valve stenosis was the first form of heart disease studied with echocardiography.[1] Although the echocardiographic features of acquired mitral stenosis have been described in detail,[2–6] there have been relatively few studies of congenital mitral stenosis.[7–12] Compared with its acquired counterpart, congenital mitral stenosis is less common, more often associated with other cardiac defects and more variable in anatomy.[13–18] Whereas acquired mitral stenosis is almost invariably due to leaflet thickening and commissural fusion, congenital left ventricular inflow obstruction may result from anomalies of the papillary muscles, chordae tendineae or mitral leaflets or from a supravalve mitral membrane. Because these malformations are indistinguishable clinically, and often cannot be differentiated with cardiac catheterization or angiography, they are collectively referred to as forms of congenital mitral stenosis.[15–18] In this study the term "mitral stenosis" includes any of these abnormalities of the mitral valve apparatus. More specific terminology is used when the anatomy of the lesion was documented at operation or autopsy.

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This study was undertaken to define the echocardiographic features of congenital mitral stenosis. We attempted to determine (1) if the various anatomic types of congenital mitral stenosis can be distinguished with single crystal M mode echocardiography, (2) if the severity of the inflow obstruction can be predicted, and (3) if mitral stenosis can be detected in the presence of associated cardiac lesions.

The echocardiograms of patients with documented mitral stenosis were compared with those of normal children. Because many of the patients with mitral stenosis had associated coarctation of the aorta or ventricular septal defect, their echocardiograms were also compared with those of 22 patients with isolated ventricular septal defect and 16 patients with isolated coarctation of the aorta.

Material and Methods

Patient Groups

Normal children: These were 145 normal children previously studied in our laboratory whose echocardiograms were reviewed. The subjects were 1 day to 19 years old at the time of study and had no heart disease as judged from the history and physical examination.

Congenital mitral stenosis: This group consisted of 30 children aged 9 days to 15 years. None had a history of rheumatic fever. In all 30, the presence of congenital heart disease was first detected in infancy, and the diagnosis was established at cardiac catheterization and angiography. In 12, the presence and nature of the mitral valve lesion was confirmed at operation (8 patients) or autopsy (4 patients).

Six of 12 patients whose mitral valve was inspected at operation or autopsy had a supravalve mitral membrane. Two of these six patients also had parachute mitral valve deformity (single papillary muscle). Of the six patients without supravalve mitral membrane, one had isolated parachute mitral valve deformity, and five had isolated fusion of the valve leaflets.

Twenty-eight of the 30 patients with mitral stenosis had one or more additional congenital cardiac defects. These included coarctation of the aorta (19 patients), ventricular septal defect (11 patients), aortic valve stenosis (12 patients), transposition of the great arteries (2 patients), double outlet right ventricle (2 patients) and aortic valve insufficiency (2 patients).

The severity of the mitral stenosis was considered mild if the pulmonary arterial wedge or left atrial *A* wave to left ventricular end-diastolic pressure gradient was less than 10 mm Hg, moderately severe if the gradient was 10 to 20 mm Hg and severe if the gradient was greater than 20 mm Hg. Calculation of mitral valve area is the optimal method for determining the severity of mitral stenosis; however, because this calculation could not be made with confidence in patients with complex intracardiac lesions, we arbitrarily grouped the patients according to the mitral valve gradient.

In the patients with mitral stenosis and a coexistent left to right shunt, the ratio of pulmonary to systemic blood flow ranged from 1.2 to 2.5 (mean 1.7), and the pulmonary arterial wedge or left atrial *A* wave to left ventricular end-diastolic pressure gradient ranged from 6 to 27 mm Hg (mean 13.6).

Isolated ventricular septal defect: This group consisted of 22 patients, aged 7 weeks to 22 years. The ratio of pulmonary to systemic blood flow ranged from 1.0 to 2.8 (mean 1.8), and the gradient across the mitral valve ranged from 0 to 4 mm Hg (mean 1.3).

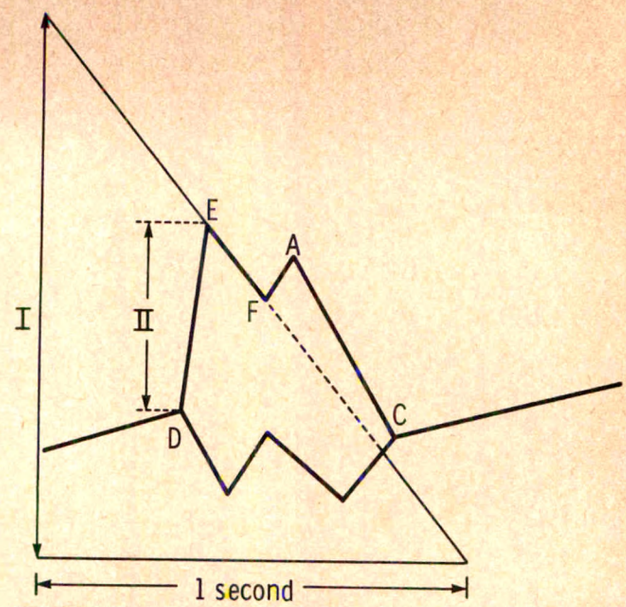


FIGURE 1. Diagram of mitral valve motion illustrating the method used to measure amplitude of excursion of the anterior leaflet (II) and the rate of early diastolic closure or E-F slope (I). Note the large M pattern produced by the anterior leaflet and the small W pattern produced by the posterior leaflet.

Coarctation of the aorta: These 16 patients were 2 to 17 years old. No patient was included in this group unless the mitral valve appeared normal on angiography and there was no mitral valve gradient.

Analysis of Echocardiogram

Qualitative analysis: *The mitral valve echograms were analyzed with regard to the following:* (1) the direction of movement of the posterior mitral leaflet in diastole; (2) the presence of mitral valve reopening associated with atrial contraction (because the so-called *A* wave is usually not discernible in normal subjects with a rapid heart rate, this assessment was made only in subjects with a heart rate less than 120 beats/min); and (3) the presence of diastolic vibration or fluttering of the mitral valve leaflets.

Quantitative analysis: *The following measurements were made from the mitral echogram in each patient:* (1) The amplitude of excursion of the anterior leaflet. This was measured at the point of maximal excursion of the leaflet and was considered to be the distance traversed by the leaflet as it opened at the start of diastole (the vertical distance from the D point to a horizontal line passing through the E point (Fig. 1). (2) The rate of early diastolic closure of the anterior leaflet (E-F slope). This measurement (Fig. 1) was made only if the passive closure of the valve in early diastole could be clearly separated from the active closure produced by ventricular systole. In some cases these events could be separated by the occurrence of mitral reopening after atrial contraction; in others the distinction could be made on the basis of the acceleration in the rate of closure that occurred with ventricular contraction.

All echocardiograms were performed with a Hoffrel model 101 Ultrasonoscope interfaced to a Honeywell 1856 strip chart recorder. Transducers of 2.25 or 3.5 megahertz were used.

Results

Prediction of the anatomy of the mitral valve apparatus (12 patients with mitral stenosis and documented anatomy): Review of the echocardiograms of the 12 patients with mitral stenosis in whom the site of inflow obstruction was determined at operation or surgery indicated that it was not possible to determine the anatomy of the mitral obstructive lesion from the echocardiogram. In particular, the supravalve mitral membrane could not be distinguished from other forms of congenital mitral stenosis (Table I). In one patient with supravalve membrane, a linear echo was present between the anterior and posterior mitral leaflets (Fig. 2). However, in five other patients with this lesion, no abnormal echoes were present, either between the mitral leaflets or in the left atrium (Fig. 3, A and B). Similarly, there were no echographic features unique to the parachute mitral valve deformity or to commis-

TABLE I

Comparative Echographic Features of Various Forms of Congenital Mitral Stenosis

Echographic Findings	Anatomy of Mitral Lesions Noted at Autopsy or Surgery: Valve Stenosis (commissural fusion)	Supravalve Membrane and Parachute Mitral Valve	Supravalve Mitral Membrane	Parachute Mitral Valve
Qualitative				
A wave present*	1/4	1/1	1/1	0/1
DAMPL	2/5	1/2	4/4	1/1
Vibration	3/5	2/2	4/4	0/1
Quantitative				
Decreased excursion	2/5	0/2	1/4	1/1
Decreased E-F slope	5/5	1/2	3/4	0/1

* Assessed only if heart rate was less than 120 beats/min.
DAMPL = diastolic anterior motion of posterior leaflet.

TABLE II

Echocardiographic Analysis of Mitral Valve Motion

Group	no. of Cases	Age Range (yr)	Body Weight Range (kg)	Mitral Valve Gradient* (mm Hg)	Qualitative Aspects: *A* Wave Present†	DAMPL	Vibration	Quantitative Aspects: Decreased Excursion	Decreased E-F Slope
Normal	145	0.002–19	3–69	...	107/107	0/145	12/145	0/145	0/145
Mitral stenosis	30	0.02–16	3–50	13.6 ±1.1	8/21	17/30	21/30	6/30	19/30
Ventricular septal defect	22	0.13–22	3–76	1.3 ±0.3	15/15	1/21	8/22	0.22	0/22
Coarctation of aorta	16	2–7	13–60	0.3 ±0.25	13/13	0/16	2/16	4/16	1/16

* Values expressed as mean ± standard error of the mean.
† Presence or absence ascertained only if heart rate was less than 120 beats/min.
DAMPL = diastolic anterior motion of posterior leaflet.

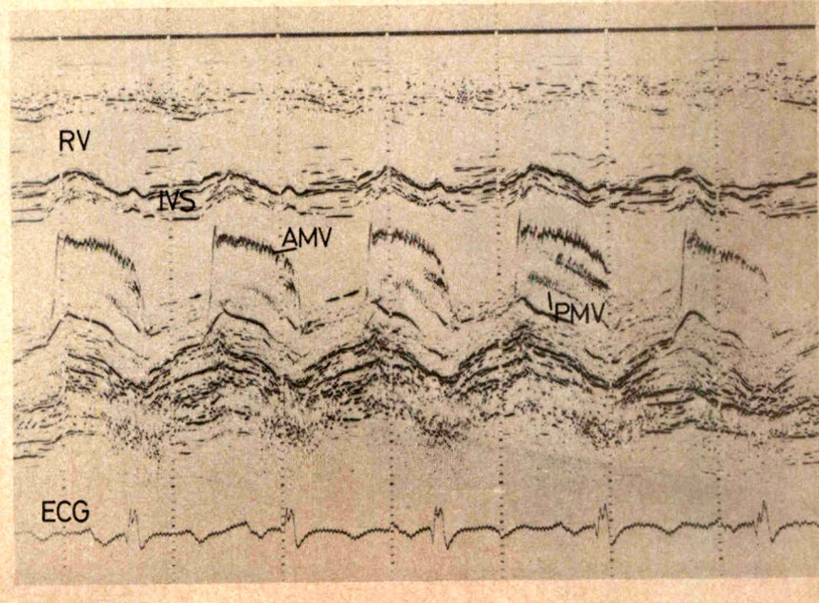


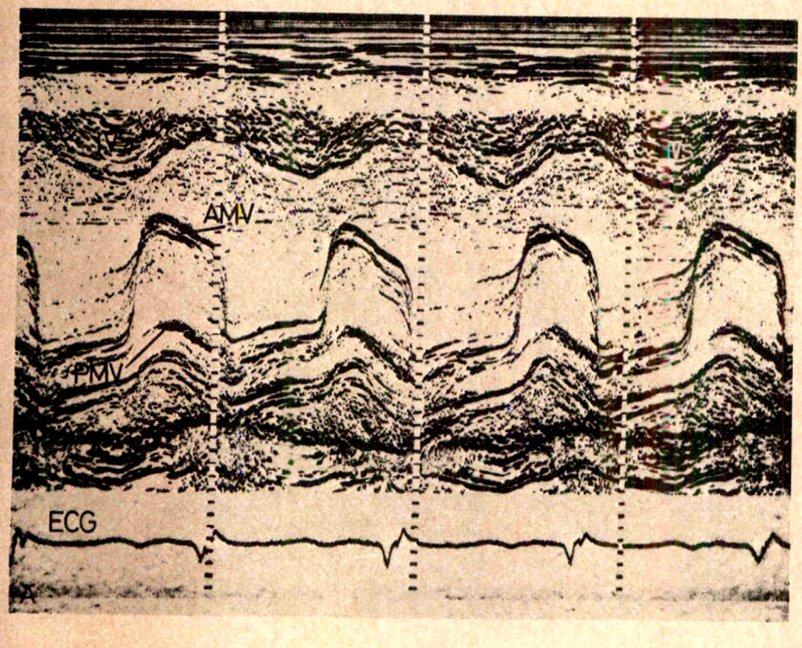
FIGURE 2. A coarse pattern of diastolic vibration is apparent in the mitral echogram from this 12 year old boy with a supravalve mitral membrane and ventricular septal defect. The membrane itself could not be identified with certainty, although it may be represented by the echo between the anterior and posterior leaflets on the third and fourth beats. AMV = anterior mitral leaflet; ECG = electrocardiogram; IVS = interventricular septum; PMV = posterior mitral leaflet; RV = right ventricle.

sural fusion. Diastolic anterior motion of the posterior leaflet, absent *A* wave, reduced excursion and reduced E-F slope occurred in some but not all patients with these lesions (Table I).

Qualitative analysis of mitral valve motion (all patients): One or more qualitative abnormalities of mitral valve motion were present in 28 of the 30 patients with hemodynamic evidence of mitral stenosis (Table II).

Movement of posterior leaflet: In 17 patients, there was paradoxical anterior motion of the posterior mitral leaflet during diastole that produced a linear echo parallel to that of the anterior leaflet (Fig. 4 and 5). This pattern of motion occurred in only one patient with ventricular septal defect and in no patient with coarctation of the aorta. In all normal subjects there was appropriate posterior movement of the posterior leaflet in diastole. In normal subjects with a heart rate of less than 120 beats/min, relative anterior movement of the posterior leaflet occurred at the end of the passive ventricular filling period. However, this relative anterior movement was followed by posterior movement associated with atrial systole. This normal movement resembles a "W" (Fig. 1).

Vibration of leaflets: Diastolic vibration of one or both mitral valve leaflets was present in 21 of the 30



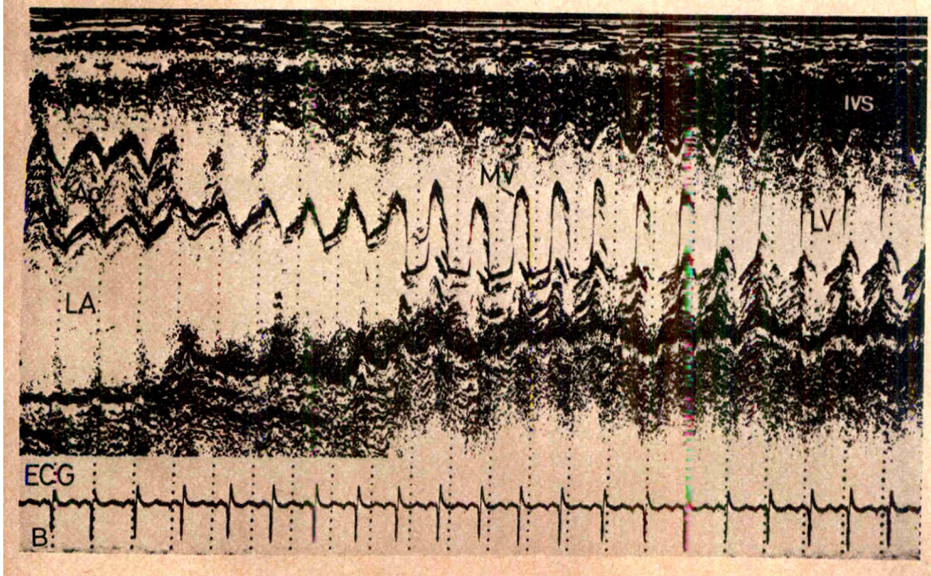


FIGURE 3. These recordings from a 2 year old boy with a ventricular septal defect and a supravalve mitral membrane illustrate the difficulty in predicting the nature of the mitral obstructive lesion from the echocardiogram. **A,** the recording of mitral valve motion shows a reduced E to F slope and initial anterior motion of the posterior mitral leaflet (PMV). **B,** although a discrete supravalvular mitral membrane was found at operation, no abnormal echoes are seen posterior to the left ventricular outflow tract. Ao = aorta; LA = left atrium; LV = left ventricle; MV = mitral valve; other abbreviations as in Figure 2.

patients with mitral stenosis (Fig. 2, 4 and 6). Similar vibration was observed in 8 of the 22 patients with ventricular septal defect and in 2 of the 16 with aortic coarctation. This vibration, although of low amplitude, was also present in 12 of the 145 normal children. Thirteen patients with mitral stenosis had leaflet vibration as well as anterior motion of the posterior leaflet in diastole. This vibration appeared to be unrelated to the type of mitral valve obstruction. The most prominent vibration was seen in a 12 year old boy with a supravalve mitral membrane (Fig. 2).

Quantitative analysis of mitral valve motion (all patients): *Excursion of anterior leaflet:* In normal children there was a linear relation between the excursion of the anterior leaflet of the mitral valve and the cube root of body weight.[19] The amplitude of excursion of the anterior leaflet of the mitral valve was normal (that is, within 2 standard deviations of the normal mean as determined from body weight) in 24 of the 30 patients with mitral stenosis and in 12 of the 16 patients with aortic coarctation. Mitral excursion was normal in all patients with ventricular septal defect (Table II).

E to F slope: In normal children the mitral E-F slope increased with body weight, although there was a wide range of E-F slopes for any given weight. The E-F slope of the anterior leaflet was below the normal range in 19 of 30 patients with mitral stenosis (Fig. 7). No patient with ventricular septal defect and only one patient with aortic coarctation had an abnormal E-F slope (Table II).

Determination of severity of mitral stenosis (all patients with mitral stenosis): Patients with severe mitral stenosis (gradient greater than 20 mm Hg) tended to have a greater decrease in E-F slope than

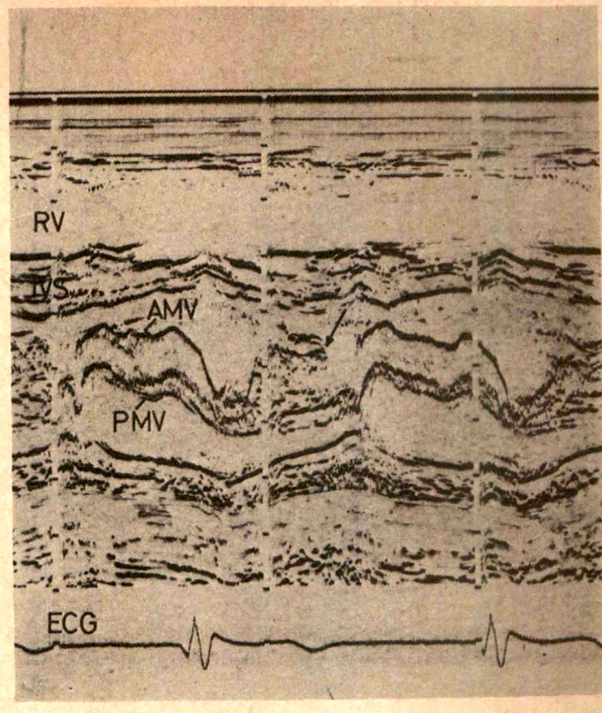


FIGURE 4. Mitral valve echogram in a 5 year old boy with a parachute mitral valve and moderately severe obstruction to mitral flow (gradient 12 mm Hg). A coarctation of the aorta had been resected in infancy. Both mitral leaflets appear to vibrate in diastole. After a brief posterior motion in early diastole, the posterior mitral leaflet (PMV) moves anteriorly and follows the motion of the anterior leaflet. The mass of echoes moving anteriorly in systole **(arrow)** presumably results from the simultaneous recording of the mitral leaflets and a large single papillary muscle. The latter was noted on angiography to have a prominent anterior motion in systole. Abbreviations as in Figure 2.

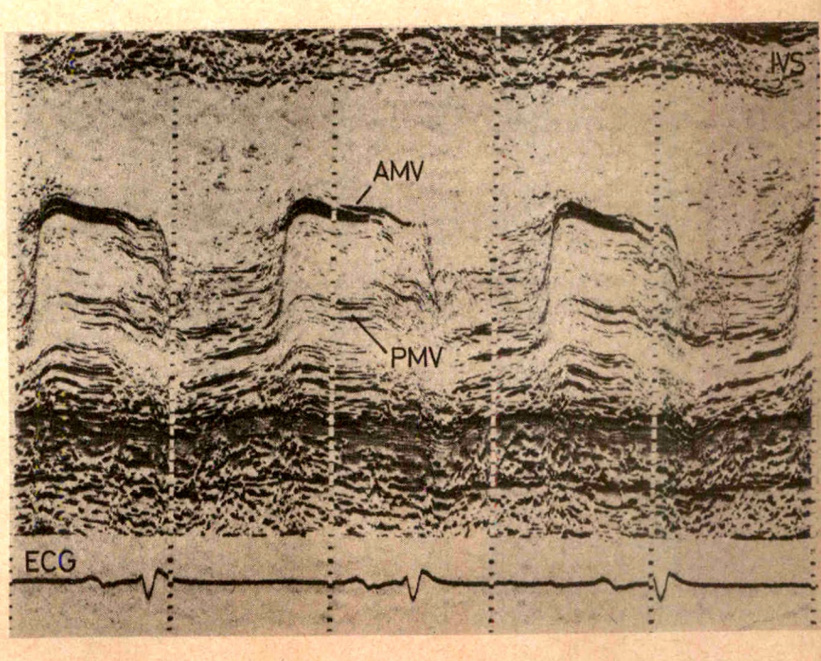


FIGURE 5. Mitral valve echogram in a 10 year old boy with mitral stenosis and double outlet right ventricle. The posterior leaflet (PMV) moves anteriorly in early diastole, and the E-F slope is reduced (16 mm/sec). There is no vibration of the valve leaflets. This combination is similar to the findings in acquired mitral stenosis. Abbreviations as in Figure 2.

patients with milder degrees of stenosis (Fig. 7). In addition, diastolic anterior movement of the posterior leaflet was more common in the patients with severe stenosis (Table III). In general, however, it was not possible to predict the severity of the stenosis from any of the qualitative or quantitative aspects of valve motion.

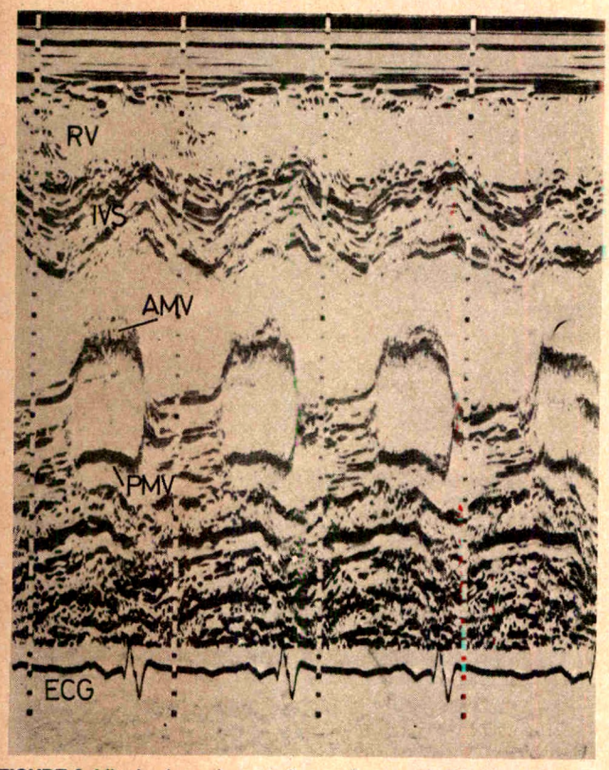


FIGURE 6. Mitral valve echogram from a 5 year old girl with moderately severe mitral stenosis (diastolic gradient 11 mm Hg). There is fine vibration of both leaflets. The posterior leaflet moves normally, but the E-F slope is reduced. Abbreviations as in Figure 2.

Mitral stenosis with left to right intracardiac shunt: In this study, all seven patients with mitral stenosis and a coexistent left to right intracardiac shunt had a mitral valve gradient greater than the gradient in patients with isolated ventricular septal defect. The two groups had left to right shunts of similar magnitude. Parodoxic anterior motion of the posterior mitral valve leaflet occurred in only one patient with isolated ventricular septal defect but in five of seven patients with coexistent mitral stenosis (Table IV). Although patients in each group had vibration of the mitral valve leaflets, it was more common in patients with mitral stenosis and a left to right shunt than in those with a left to right shunt alone.

Mitral stenosis with coarctation of the aorta: Congenital abnormalities of the mitral valve apparatus, especially of the papillary muscles, are often present in patients with coarctation of the aorta.[20] Six of our 16 patients with isolated coarctation of the aorta had an abnormal mitral echogram, despite the absence of hemodynamic or angiocardiographic evidence of mitral stenosis. The most common echocardiographic findings in these 16 patients were reduction of the excursion of the anterior leaflet (4 patients) and leaflet vibration (2 patients). Of 19 patients with coarctation and associated mitral stenosis, 4 had decreased excursion of the anterior leaflet of the mitral valve, and 15 had leaflet vibration. In addition, patients with coexistent mitral stenosis exhibited diastolic anterior motion of the posterior mitral valve leaflet (10 of 19) and absence of the *A* wave (7 of 13), findings not present in any patient with isolated coarctation.

Discussion

In 1955, Edler[2] described the echographic features of mitral stenosis as a reduced E-F slope and decreased opening excursion. Other investigators[6] have reported variable accuracy in quantifying the degree of the ste-

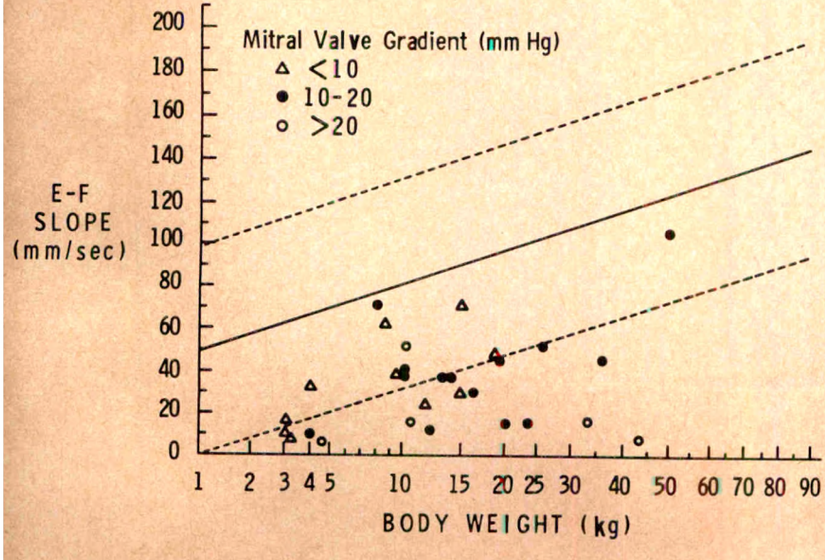


FIGURE 7. Graph depicting the E-F slope of the anterior mitral leaflet in 29 patients with congenital mitral stenosis and 145 normal subjects. The **solid diagonal line** represents the calculated regression line for the 145 normal subjects. The **dashed lines** indicate 2 standard errors of the estimate above and below the regression line and include 95 percent of the normal subjects and 20 percent of the patients with mitral stenosis.

TABLE III

Echocardiographic Findings Related to Severity of Mitral Valve Obstruction in Patients With Mitral Stenosis

Mitral Valve Gradient Range (mm Hg)	no. of Cases	Qualitative Aspects			Quantitative Aspects	
		A Wave Present	DAMPL	Vibration	Decreased Excursion	Decreased E-F Slope
<10	11	4	5	8	2	5
10–20	12	7	7	9	3	8
>20	5	2	4	3	1	4

DAMPL = diastolic anterior motion of posterior leaflet.

TABLE IV

Mitral Valve Echocardiographic Findings in Patients With Left to Right Intracardiac Shunts

	no. of Cases	Qualitative Aspects			Quantitative Aspects	
		A Wave Present	DAMPL	Vibration	Decreased Excursion	Decreased E-F Slope
Ventricular septal defect and mitral stenosis	7	2/5	5/7	5/7	0/7	2/7
Isolated ventricular septal defect	22	15/15	1/21	8/22	0/21	0/22

DAMPL = diastolic anterior motion of posterior leaflet.

nosis from the mitral echogram. Duchak et al.[3] called attention to the importance of recording the motion of the posterior mitral leaflet in the diagnosis of mitral stenosis. Although in normal subjects the anterior and posterior leaflets move in opposite directions during early and late diastole, the characteristic feature of acquired mitral stenosis is diastolic anterior motion of the posterior leaflet. Although some exceptions have been reported, this paradoxical motion of the posterior leaflet helps to distinguish acquired mitral stenosis from other conditions producing decreased mitral excursion and reduced rate of diastolic closure.

Echocardiogram in specific types of mitral valve obstruction: In several previous reports it has been suggested that the specific anatomic types of left ventricular inflow obstruction may be diagnosed with echocardiography. Chung et al.[10] demonstrated an abnormal echo behind the mitral valve in a patient with a supravalve membrane. LaCorte et al.[11] demonstrated an abnormal echo posterior to the mitral leaflets in two patients with this lesion. We were unable to duplicate these findings. In five of our six patients with confirmed supravalve membrane there were no abnormal echoes, either behind the aorta or between the mitral leaflets. In one patient (Fig. 2) three parallel echoes could be recorded from the mitral valve region, and one of these echoes could have been produced by the supravalve ring itself. Similarly, there was no consistent pattern of mitral valve motion in patients with the parachute mitral valve deformity or isolated leaflet fusion.

Detection of mitral stenosis in presence of other congenital lesions: Congenital mitral stenosis is rarely an isolated lesion and is frequently associated with either a ventricular septal defect or left ventricular outflow obstruction. The results of our study indicate that mitral stenosis can generally be detected in the presence of coexistent lesions. Diastolic anterior motion of the posterior mitral leaflet and absence of the *A* wave were the findings most useful in distinguishing patients with mitral stenosis and ventricular septal defect from those with isolated ventricular septal defect. Although mitral valve excursion was reduced in 4 of 16 patients with isolated coarctation, abnormal posterior leaflet motion and an absent *A* wave were present only when there was coexistent mitral obstruction.

Diastolic vibration of both mitral leaflets: This was observed in 21 of the 30 patients with mitral stenosis. This motion was similar to that seen in the anterior mitral leaflet in patients with aortic insufficiency[21] and aorticopulmonary transposition.[21–23] Similar leaflet vibration occurred in some patients with increased blood flow across the mitral valve due to a ventricular septal defect, and similar vibration, although of lesser amplitude, was seen in 8 percent of the normal children. Diastolic vibration of the mitral valve leaflets was unrelated to the type or severity of mitral obstruction in this study. We speculate that this vibration results from turbulent blood flow through the mitral orifice in the presence of pliable leaflets. To our knowledge, leaflet vibration has not been described in the acquired forms of mitral stenosis, which are usually associated with thickened valve leaflets.

Diagnostic implications: We found the echocardiogram to be more useful in detecting the presence of congenital mitral stenosis than in estimating its severity or delineating the precise anatomy of the mitral valve. Because this lesion is rare and usually associated with other congenital cardiac malformations, it may be overlooked at the time of clinical examination or even at cardiac catheterization. The echocardiographic demonstration of a decreased E-F slope, diastolic anterior motion of the posterior mitral leaflet and absence of the *A* wave should alert the clinician to the presence of mitral stenosis.

References

1. **Edler I, Hertz CH:** The use of ultrasonic reflectoscope for the continuous recording of the movement of heart walls. Kungl Fysiog Sallsk Lung Fordhandl 24:40–58, 1954
2. **Edler I:** The diagnostic use of ultrasound in heart disease. Acta Med Scand [Suppl] 308:32–36, 1955
3. **Duchak JM Jr, Chang S, Feigenbaum H:** The posterior mitral valve echo and the echocardiographic diagnosis of mitral stenosis. Am J Cardiol 29:628–632, 1972
4. **Levisman JA, Abbasi AS, Pearce ML:** Posterior mitral leaflet motion in mitral stenosis. Circulation 51:511–514, 1975
5. **Gustafson A:** Correlation between ultrasoundcardiography, hemodynamics and surgical findings in mitral stenosis. Am J Cardiol 19:32–41, 1967
6. **Cope GD, Kissio JA, Johnson ML, et al:** A reassessment of the echocardiogram in mitral stenosis. Circulation 52:664–670, 1975
7. **Lundstrom NR:** Echocardiography in the diagnosis of congenital mitral valvotomy. Circulation 46:44–54, 1972
8. **Lundstrom NR:** Ultrasoundcardiographic studies of the mitral valve region in young infants with mitral atresia, mitral stenosis, hypoplasia of the left ventricle and cor triatriatum. Circulation 45: 324–334, 1972
9. **Solinger R, Elbl F, Minhas K:** Echocardiographic features of the hypoplastic atrioventricular valve (abstr). Circulation 45:Suppl II: II-224, 1972
10. **Chung KS, Manning JA, Lipchik EO, et al:** Isolated supravalvar stenosing ring of left atrium: diagnosis before operation and successful surgical treatment. Chest 65:25–28, 1974
11. **LaCorte M, Harada K, Williams R:** Echocardiographic features of congenital left ventricular inflow obstruction. Circulation 54: 562–566, 1976
12. **Keutel J:** Echocardiographic diagnosis and evaluation of rare congenital anomalies. In, Ultrasonics in Medicine (Kazner E, de Vlieger M, Muller H, et al, ed). Amsterdam, Oxford, Excerpta Medica (New York, American Elsevier), 1975, p 231–244
13. **Shone JD, Sellers RD, Anderson RC, et al:** The developmental complex of "parachute mitral valve," supravalvar ring of left atrium, subaortic stenosis and coarctation of aorta. Am J Cardiol 11: 714–725, 1963
14. **Van der Horst RL, Hastreiter AR:** Congenital mitral stenosis. Am J Cardiol 20:773–783, 1967
15. **Davachi F, Moller JH, Edwards JE:** Diseases of the mitral valve in infancy; an anatomic analysis of 55 cases. Circulation 43: 565–579, 1971
16. **Glancy DL, Chang MY, Dorney ER, et al:** Parachute mitral valve; furthur observations and associated lesions. Am J Cardiol 27: 309–313, 1971
17. **Kahlili KG, Shapiro I, Kilman JW:** Congenital mitral stenosis. J Thorac Cardiovasc Surg 70:40–45, 1975
18. **Nadas A, Fyler D:** Pediatric Cardiology. Philadelphia, WB Saunders, 1972, p 509
19. **Gutgesell HP, Paquet M:** Atlas of Pediatric Echocardiography. Hagerstown, MD, Harper & Row, p 207
20. **Rosenquist G:** Congenital mitral valve disease associated with coarctation of the aorta. Circulation 49:985–992, 1974
21. **Feigenbaum H:** Echocardiography. Philadelphia, Lea & Febiger, 1973, p 65
22. **Hagler DJ, Tajik AJ, Ritter DG:** Fluttering of atrioventricular valves in patients with d-transposition of the great arteries after Mustard operation: an echographic observation. Mayo Clinic Proc 50:69–75, 1975
23. **Nanda NC, Stewart S, Gramiak R, et al:** Echocardiography of the intra-atrial baffle in dextrotransposition of the great arteries. Circulation 51:1130–1135, 1975

Combined Nitroprusside-Dopamine Therapy in Severe Chronic Congestive Heart Failure

Dose-Related Hemodynamic Advantages Over Single Drug Infusions

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To assess the circulatory effects of afterload reduction and inotropism individually and in combination as rational therapy for refractory heart failure, nitroprusside and dopamine were administered to 13 patients with severe cardiac decompensation. Dopamine at average doses of 3 and 7 μg/kg per min produced increases in cardiac output and reductions in peripheral resistance. At doses of 15 μg/kg per min, dopamine increased heart rate, peripheral arterial pressure and side effects. Nitroprusside alone decreased left-sided filling pressures and increased cardiac output. When the agents were administered together, the increases in cardiac output were significantly greater than with either agent alone and there was physiologic improvement in overall circulatory function. The relations among changes in afterload (systemic impedance), preload (filling pressures) and cardiac index help to explain the salutary effects of combined therapy in patients with refractory heart failure.

Recent reports[1–3] have documented the improvement in left ventricular function attainable with therapy to reduce peripheral vascular resistance or impedance in chronic congestive heart failure. In selected groups of patients, administration of sodium nitroprusside,[4,5] phentolamine,[5–7] sublingual nitroglycerin,[8–10] nitroglycerin ointment,[11] isosorbide dinitrate[12,13] or hydralazine[14,15] has resulted in improved circulatory performance with only small changes in heart rate or arterial pressure. These drugs decrease left ventricular impedance (afterload) or left ventricular filling pressure (preload), or both, without directly altering left ventricular contractile state. In contrast, catecholamines such as dopamine increase cardiac output in chronic congestive heart failure at least in part by augmenting left ventricular contractility.[16,18] In larger doses, catecholamines produce vasoconstriction, with a resulting increase in left ventricular impedance.[19,20] Thus, these two classes of drugs improve circulatory performance by distinctly different mechanisms.

Despite the availability of these agents, there is a need for more effective cardiotonic drug therapy in many states of acutely depressed cardiac function, including chronic refractory congestive heart failure, pulmonary edema, cardiogenic shock and postoperative left ventricular failure. One method that might achieve improved left ventricular function is to combine the vasodilator action of nitroprusside with the inotropic effect of dopamine. In this study, we compared the maximal hemodynamic improvement achieved with optimal doses of each of these drugs with the results of their combined administration in identical doses.

Patients with chronic refractory congestive heart failure were studied because they would not be expected to manifest spontaneous changes in left ventricular function during the 2 to 3 hour protocol period, in

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contrast to patients studied postoperatively or after acute myocardial ischemia. Patients with acute myocardial infarction were also excluded because of the unpredictable effect of this drug combination on regional coronary blood flow, left ventricular metabolic demands and infarct size.[21–25]

Methods

Patients: Thirteen patients with clinical and radiographic evidence of severe congestive heart failure (New York Heart Association class IV[26]) refractory to conventional therapy of digitalis and diuretic drugs were studied. All patients had a cardiac index of less than 2.5 liters/min per m^2 and a pulmonary arterial wedge pressure greater than 20 mm Hg at rest. The origin of the heart disease was ischemic in six patients, viral in two and idiopathic in five. Patients with primary valvular heart disease, primary pulmonary disease, acute ischemia, chest pain or a history of acute myocardial infarction within the past 3 months were excluded. Patients were studied in the postabsorptive state in a special procedure room or cardiac catheterization laboratory. Informed consent was obtained in every case in accord with the Stanford University Medical Committee on the Use of Human Subjects in Research. All vasodilator, antihypertensive and diuretic medications were withheld 12 hours before each study.

Control hemodynamic measurements: Right heart catheterization was performed using a no. 7F triple lumen Swan-Ganz flow-directed balloon-tipped catheter or a no. 7F Cournand catheter inserted percutaneously through an antecubital or femoral vein. Arterial pressure was monitored with an intraluminal catheter inserted into the brachial or radial artery or into the descending aorta. All pressures were measured using Statham pressure transducers with the patient supine. Zero reference was the mid axillary line.

Pulmonary arterial diastolic and pulmonary arterial wedge pressures were compared at the beginning of the study. If the two pressures were within 3 mm Hg of each other, pulmonary arterial diastolic pressure was used to determine left ventricular filling pressure during the remainder of the study. Otherwise, pulmonary arterial wedge pressure was measured separately for each drug condition. In five patients, right atrial pressure was also measured at each drug dose. In the other eight patients, right atrial pressure was measured only during the control period and was subsequently estimated by assuming that during each drug infusion it changed in the same proportion as pulmonary arterial wedge pressure. In the five patients with measurements available, this assumption was accurate within 2 mm Hg.

All patients had resting control cardiac output determinations using the Fick principle. In seven patients, simultaneous determinations of cardiac output, using the thermodilution technique with 10 cc of iced 5 percent dextrose in water, were reproducible and accurate within ±10 percent of the value determined with the direct Fick method under control conditions. In these patients, further cardiac output determinations were made in triplicate using a standard thermodilution technique. Although at low cardiac output levels Fick determinations may be more reproducible, thermodilution output measurements were repeated to obtain good agreement in steady-state conditions. The agreement between thermodilution output values was held to 5 percent, or the data were discarded and the measurements repeated. The increases measured during drug infusions far exceeded this reproducibility. In the remaining six patients, arteriovenous oxygen content difference was determined during each drug infusion. Oxygen consumption was measured at rest and during the maximal dose of each drug and drug combination. Cardiac output was calculated with the Fick principle using the simultaneously determined oxygen consumption or the average of the previous and subsequent oxygen consumption data.

Protocol for drug administration and measurements: On completion of control measurements, dopamine or nitroprusside infusion was begun, using a variable speed infusion pump. Each drug at each dose level was infused sequentially for at least 12 minutes to reach steady-state conditions; then, cardiac output, heart rate, pulmonary arterial pressure, pulmonary wedge pressure and systemic arterial pressure were recorded during continued drug administration. When these measurements were completed, the next drug dose was given and hemodynamic measurements were repeated in the same manner. Dopamine was infused at three fixed doses: 3.5, 7.0 and 15 μg/kg per min. In six patients the latter dose was not administered because of excessive side effects during the 7

TABLE I

Clinical Characteristics of Patients Studied

Case no.	Age (yr)	Previous Cardiac Catheterization	Origin of Heart Disease	Degree of Mitral Regurgitation	Previous Cardiovascular Drug Therapy	Nitroprusside Dose (μg/kg per min)
1	51	Yes	Ischemic	Moderate	Digoxin, furosemide, alpha methyldopa, Coumadin, potassium chloride, isosorbide dinitrate	2.0
2	19	Yes	Viral	Mild	Digoxin, furosemide, potassium chloride, nitroglycerin ointment	0.6
3	44	No*	Ischemic	Moderate	Digoxin, furosemide, isosorbide dinitrate	1.6
4	46	No*	Ischemic	Mild	Digoxin, furosemide, Coumadin, potassium chloride	0.5
5	43	No*	Idiopathic	Moderate	Digoxin, furosemide, potassium chloride	1.4
6	46	Yes	Ischemic	Moderate	Digoxin, furosemide, isosorbide dinitrate, hydralazine, procainamide	1.5
7	17	Yes	Idiopathic	Moderate	Digoxin, furosemide, potassium chloride	1.0
8	47	Yes*	Idiopathic	Severe	Digoxin, furosemide, potassium chloride	0.5
9	41	Yes	Ischemic	Mild	Digoxin, furosemide, Coumadin, nitroglycerin ointment	1.0
10	52	Yes	Idiopathic	Mild	Digoxin, furosemide, isosorbide dinitrate, potassium chloride	1.6
11	38	Yes	Ischemic	Moderate	Digoxin, furosemide, potassium chloride	1.0
12	58	Yes	Idiopathic	Mild	Digoxin, furosemide, isosorbide dinitrate, hydralazine, prazosin	1.3
13	46	Yes	Viral	Moderate	Digoxin, furosemide, potassium chloride, nitroglycerin ointment	0.8
Mean	41.4	...	...	...	...	1.1

* Left ventricular angiogram performed after drug infusions.

μg/kg per min infusion. Nitroprusside infusion was begun at a rate of 0.5 μg/kg per min, and the dose was adjusted as necessary to provide a decrease in pulmonary arterial wedge pressure of 5 to 15 mm Hg while maintaining a mean arterial pressure greater than 50 mm Hg. The mean nitroprusside dose was 1.1 μg/kg per min (range 0.5 to 2.0).

After administration of the first drug was completed, the patient was allowed a 15 minute recovery period before he received the second drug in the manner described. Seven patients received dopamine first, and six received nitroprusside first. After each drug was administered individually, with hemodynamic monitoring, identical dopamine infusions were repeated (two or three doses) in combination with the same dose of nitroprusside that the patient had received earlier.

Calculations and statistical analysis: Four derived hemodynamic variables were calculated. Systemic and pulmonary mean pressures were determined electronically. Systemic vascular resistance (SVR) was determined as SVR = (MAP − RAP)/CO, where MAP = mean arterial pressure, RAP = right atrial pressure and CO = cardiac output. Similarly, pulmonary vascular resistance (PVR) was calculated as PVR = (MPAP − PAW)/CO, where MPAP = mean pulmonary arterial pressure, PAW = pulmonary arterial wedge pressure and CO = cardiac output. Both resistance values were expressed in arbitrary units. The double (pressure-rate) product (DP) as utilized by others, an index of left ventricular oxygen demand, was determined as DP = SBP × HR, where SBP = systolic blood pressure and HR = heart rate. Stroke volume index (SVI) was calculated as SVI = CO/HR, where CO = cardiac output and HR = heart rate.

Statistical analysis was performed with Student's paired *t* test because each patient served as his own control. Several comparisons were made. Each hemodynamic variable at each drug dose was compared with the control value in the same patients. In addition, the effect of each dose of dopamine was compared with the effect of nitroprusside alone and that of the combination of the same dose of dopamine with nitroprusside.

Results

Patient population: The clinical characteristics of the 13 patients studied are summarized in Table I. They were a relatively young group of patients (mean age 41.4 years), and all were male. Every patient was receiving digoxin and potent diuretic therapy to which he was considered refractory on clinical grounds. Also, eight patients had received afterload-reducing agents, including isosorbide dinitrate, nitroglycerin ointment, hydralazine and prazosin. These agents were withheld for 8 hours before the study.

Although trivial mitral regurgitation was documented at cardiac catheterization in all patients, it was hemodynamically prominent in only one (Case 8). In each case the regurgitation was attributed to left ventricular dilatation and failure rather than to a primary valve lesion.

All patients had clinically severe cardiomyopathy. Five patients had two or three vessel coronary artery disease documented with coronary angiography. One patient had had a massive anterior myocardial infarction 7 months previously but had angiographically normal coronary arteries. Two patients had a viral perimyocarditis that preceded the clinical onset of congestive heart failure. Five patients had idiopathic dilated cardiomyopathy with angiographically documented normal coronary arteries. No patient had a restrictive or obstructive cardiomyopathy.

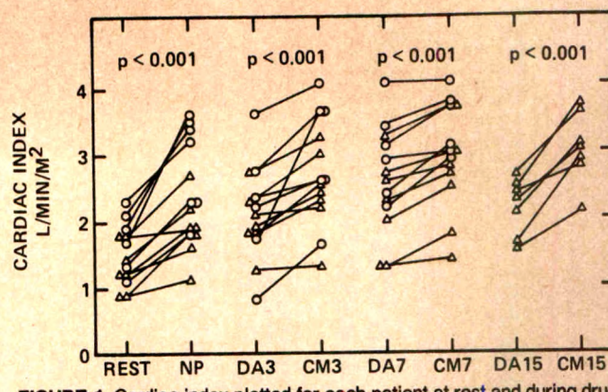

FIGURE 1. Cardiac index plotted for each patient at rest and during drug infusions. This index is significantly greater with nitroprusside than during rest, and with each combination infusion than with dopamine alone at the same dose. **Open circles** indicate patients who did not receive the 15 μg/kg per min dose of dopamine alone or in combination with nitroprusside; **open triangles** indicate patients who received this dose alone and in combined therapy. CM3, CM7, CM15 = nitroprusside in combination with dopamine at respective doses of 3, 7 and 15 μg/kg per min; DA3, DA7, DA15 = dopamine alone at respective doses of 3, 7 and 15 μg/kg per min; L/MIN/M^2 = liters/min per square meter; p = probability.

The mean value and standard error of the mean for all hemodynamic variables at rest and during each drug infusion are illustrated in Table II. The values at rest demonstrate severely compromised left ventricular function: Mean cardiac index was 1.44 liters/min per m^2 and mean left ventricular filling pressure 32 mm Hg. Pulmonary vascular resistance (4.65 units) and systemic vascular resistance (25.1 units) were both considerably elevated; stroke volume index was low (only 1.56 ml/m^2).

Cardiac index and stroke volume index: Cardiac index improved without exception from the measurement at rest in every patient at every dose of each drug (Fig. 1). Nitroprusside increased mean cardiac index 66 percent, from 1.44 to 2.39 liters/min per m^2 (P <0.001). Dopamine in the small, medium and large dose (3.5, 7 and 15 μg/kg per min) increased cardiac index by 46, 80 and 67 percent, respectively (P <0.001 for each dose). There was no significant difference between the cardiac index induced with nitroprusside alone and that induced with any dose of dopamine alone. However, with all three doses of dopamine, the addition of nitroprusside significantly improved cardiac index (average increase 31 percent; P <0.001 for each). The maximal cardiac index of 3.06 liters/min per m^2, an increase of 134 percent over the resting value, was achieved with the large dose of dopamine combined with nitroprusside (P <0.001).

Although cardiac output increased from the small to the intermediate dose of dopamine, no increase in cardiac output was obtained by increasing the dose of dopamine from 7 to 15 μg/kg per min. In fact, in three of

TABLE II

Hemodynamic Responses to Nitroprusside and Dopamine in Small, Intermediate and Large Doses

	Control (Rest)	Nitroprusside		Dopamine (3.5 μg/kg per min)		Nitroprusside Dopamine + (3.5 μg/kg per min)	
	Total Group*	Value	*P* vs. Rest	Value	*P* vs. Rest	Value	*P* vs. Rest
CI	1.44 ± 0.12	2.39 ± 0.24	<0.001	2.11 ± 0.20	<0.001	2.77 ± 0.23	<0.001
HR	95.1 ± 4.7	92.9 ± 5.0	NS	97.5 ± 5.1	NS	95.6 ± 3.6	NS
SVI	15.6 ± 1.6	25.5 ± 2.7	<0.001	21.6 ± 2.0	<0.001	28.5 ± 2.6	<0.001
MAP	80.3 ± 2.1	67.6 ± 2.9	<0.001	75.2 ± 2.3	<0.01	69.2 ± 2.0	<0.001
SVR	25.1 ± 3.0	15.0 ± 2.3	<0.001	16.1 ± 2.0	<0.001	11.3 ± 2.1	<0.001
DP	10.08 ± 0.53	8.66 ± 0.47	<0.01	10.10 ± 0.61	NS	9.09 ± 0.45	NS
PWP	32.0 ± 1.9	20.2 ± 1.8	<0.001	31.6 ± 2.2	NS	23.3 ± 1.8	<0.001
PASP	62.2 ± 5.0	41.3 ± 5.1	<0.001	58.0 ± 5.4	NS	46.8 ± 4.7	<0.001
PVR	4.65 ± 66	2.34 ± 0.42	<0.001	3.43 ± 0.51	<0.01	2.14 ± 0.30	<0.001

*All 13 patients (*P* values for the small and intermediate doses [3.5 and 7 μg/kg per min] of dopamine alone or in combination with nitroprusside refer to comparison with these values).

† Values for the seven patients given the large dose of dopamine alone or in combination with nitroprusside (*P* values in these columns refer to comparison with values at rest in this subgroup).

the seven patients receiving the latter dose, cardiac index decreased compared with the value at the intermediate dose. The mean cardiac index in the seven patients who received both the 7 and 15 μg/kg per min doses was 2.2 liters/min per m^2 at both levels.

Changes in stroke volume index were roughly parallel with changes in cardiac index under all conditions except with the large dose of dopamine. Because of the increase in heart rate, stroke volume index decreased from 21 to 19 ml/beat per m^2 when the infusion rate of dopamine was increased in seven patients from 7.0 to 15 μg/kg per min. Nitroprusside alone and the small and intermediate doses of dopamine alone increased stroke volume index by at least 40 percent over the resting value (P <0.001 for each). Furthermore, with all three combinations of dopamine and nitroprusside, stroke volume index increased over the value with dopamine infusion alone (by 33 percent [P <0.01] for small, 57 percent [P <0.001] for intermediate and 57 percent [P <0.001] for large dose infusions).

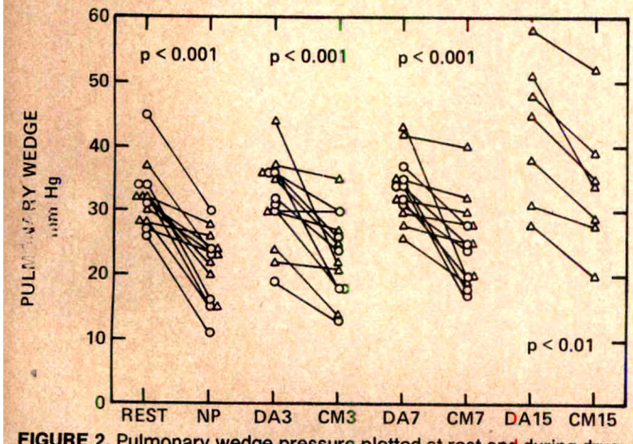

FIGURE 2. Pulmonary wedge pressure plotted at rest and during drug infusions. This pressure is significantly lower with nitroprusside than at rest, and with each combination infusion than with dopamine alone at the same dose. Abbreviations and symbols as in Figure 1.

Pulmonary wedge and pulmonary arterial pressure: Pulmonary arterial wedge pressure (Fig. 2) decreased in every patient during nitroprusside administration; the average decrease was 37 percent (from 32 to 20 mm Hg; P <0.001). In contrast, dopamine alone caused no significant change in pulmonary arterial wedge pressure at the small and intermediate doses but resulted in an increase to 30 to 40 mm Hg at the 15 μg/kg per min dose (P <0.05). The addition of nitroprusside to dopamine decreased pulmonary arterial wedge pressure from the value obtained with dopamine alone by 8.3 (P <0.001), 7.6 (P <0.001) and 6.3 mm Hg (P <0.01) for the small, medium and large doses of dopamine, respectively. As a result of these different effects, the pulmonary arterial wedge pressure with maximal combined therapy was not significantly different from the value at rest (that is, wedge pressure increased with dopamine alone and decreased to a value near control level when dopamine was combined with nitroprusside), whereas the cardiac output was greatly increased.

Changes in pulmonary arterial systolic pressure were parallel with changes in pulmonary arterial wedge pressure, decreasing by 30 percent during nitroprusside

TABLE II continued

	Dopamine (7 μg/kg per min)		Nitroprusside + Dopamine (7 μg/kg per min)		Dopamine† (15 μg/kg per min)			Nitroprusside + Dopamine† (15 μg/kg per min)	
	Value	P vs. Rest	Value	P vs. Rest	Rest Value	Value	P vs. Rest	Value	P vs. Rest
CI	2.59 ± 0.22	<0.001	2.93 ± 0.20	<0.001	1.31 ± 0.15	2.19 ± 0.16	<0.001	3.06 ± 0.16	<0.001
HR	104.6 ± 5.9	<0.05	102.9 ± 4.8	<0.05	91.7 ± 7.1	126.3 ± 7.5	<0.001	118.3 ± 5.4	<0.01
SVI	24.0 ± 2.0	<0.001	28.4 ± 2.2	<0.001	14.9 ± 1.9	18.3 ± 2.4	<0.05	25.9 ± 2.7	<0.001
MAP	84.0 ± 4.1	NS	76.5 ± 4.5	NS	81.1 ± 6.3	95.3 ± 4.6	<0.05	86.9 ± 2.5	NS
SVR	15.8 ± 1.9	<0.001	12.7 ± 1.4	<0.001	28.9 ± 4.7	19.6 ± 3.3	<0.01	13.4 ± 2.1	<0.01
DP	12.6 ± 0.58	<0.001	10.70 ± 0.42	NS	9.61 ± 0.90	16.20 ± 1.27	<0.001	13.90 ± 1.26	<0.05
PWP	33.1 ± 1.3	NS	25.5 ± 2.0	<0.05	30.4 ± 1.5	40.0 ± 3.3	<0.05	33.7 ± 4.3	NS
PASP	70.2 ± 6.1	NS	51.3 ± 5.9	<0.05	61.0 ± 3.8	87.1 ± 6.1	<0.01	73.9 ± 7.7	NS
PVR	3.13 ± 0.58	<0.001	2.09 ± 0.36	<0.001	5.33 ± 1.10	4.54 ± 0.70	NS	2.63 ± 0.42	<0.01

CI = cardiac index (liters/min per m^2); DP = double product (systolic blood pressure × heart rate [10^3 mm Hg × beats/min]); HR = heart rate (beats/min); MAP = mean arterial pressure (mm Hg); P = probability; PASP = pulmonary arterial systolic pressure (mm Hg); PVR = pulmonary vascular resistance (arbitrary units); PWP = pulmonary wedge pressure (mm Hg); SVI = stroke volume index (ml/m^2); SVR = systemic vascular resistance (arbitrary units).

infusion and showing little change with the small (3.5 μg/kg per min) dose of dopamine. However, pulmonary arterial systolic pressure increased by 13 percent to 70 mm Hg during the 7 μg/kg per min dose of dopamine, and by 45 percent to 87 mm Hg during the 15 μg/kg per min dose, causing moderate pulmonary hypertension. This pulmonary hypertension was reversed by the addition of nitroprusside to dopamine, so that there was no significant difference in pulmonary arterial systolic pressure values at rest and during combination therapy.

Pulmonary vascular resistance, which was elevated at rest, was decreased significantly by each drug, from 4.65 to 2.35 units by nitroprusside alone, and to 3.17 units by the 7 μg/kg per min dose of dopamine ($P < 0.001$). However, the greatest reduction was attained with combined nitroprusside and dopamine at 7 μg/kg per min when pulmonary vascular resistance decreased to 2.09 units ($P < 0.001$).

Heart rate and arterial pressure: Changes in heart rate during nitroprusside and small dose dopamine infusion were not significant. However, the intermediate and large dose dopamine infusions caused, respectively, an increase in heart rate of 10 percent (to 105 beats/min; $P < 0.05$) and 38 percent (to 126 beats/min; $P < 0.001$). This increase was smaller when the same doses of dopamine were combined with nitroprusside, amounting to 8 percent, to 103 beats/min ($P < 0.05$), and 29 percent, to 118 beats/min ($P < 0.01$), respectively.

Mean arterial pressure was decreased by 18 percent from 80.3 to 67.3 mm Hg with nitroprusside infusion ($P < 0.001$) and by 5 percent to 75.2 mm Hg with small dose dopamine therapy ($P < 0.01$). However, the large dose of dopamine increased mean arterial pressure by 25 percent to 95.3 mm Hg; $P < 0.05$). This increase was largely reversed with the addition of nitroprusside, resulting in a mean arterial pressure of 86.9 mm Hg ($P < 0.001$).

In summary, the changes in mean arterial pressure at the drug doses administered were much smaller than the changes in cardiac output, in spite of the well known potent effect of these drugs on blood pressure. Indeed, in our patients it can be misleading to judge the effect of these agents solely by assessing changes in systemic

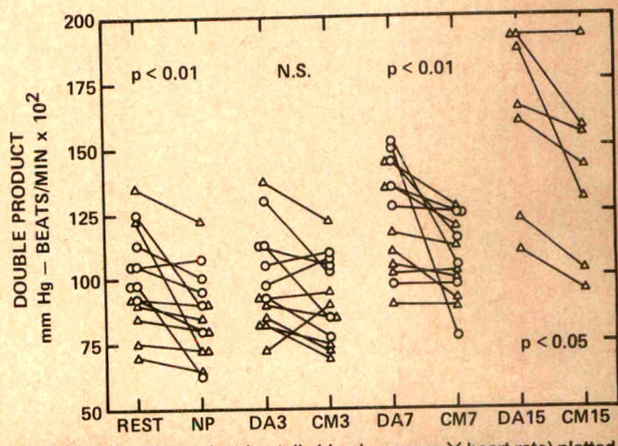

FIGURE 3. Double product (systolic blood pressure × heart rate) plotted at rest and during drug infusions. This variable is significantly lower with nitroprusside than at rest, and with the intermediate (CM7) and large dose (CM15) combinations than with dopamine alone at these doses. N.S. = not significant; other abbreviations and symbols as in Figure 1.

and pulmonary pressures without determining cardiac output. When the large dose of dopamine was combined with nitroprusside, pulmonary and arterial pressures were within 10 percent of values at rest, but cardiac output was increased by 134 percent.

The changes in double product, representing the combined effect on heart rate and systolic blood pressure, were of greater magnitude (Fig. 3). The double product was decreased with nitroprusside infusion in all but one patient (mean reduction 13 percent, from 10.08×10^3 mm Hg beats/min to 8.66×10^3 mm Hg beats/min. The small dose of dopamine alone or in combination with nitroprusside did not significantly alter double product. However, at intermediate and large doses dopamine resulted in a 27 and 69 percent increase in double product, respectively ($P < 0.001$ for each); these values decreased to 6 percent ($P < 0.01$) and 45 percent ($P < 0.05$) over control level, respectively, with the addition of nitroprusside to dopamine.

Systemic vascular resistance decreased from the value at rest in every patient at every dose of each drug (Fig. 4). The mean decrease obtained with nitroprusside was 40 percent (from 25.1 to 15.0 arbitrary units; $P < 0.001$). Dopamine alone also decreased systemic resistance (by 36 percent to 16.1 units, 37 percent to 15.8 units and 32 percent to 19.6 units at the low, medium and high levels, respectively). In the seven patients receiving both the intermediate and large doses of dopamine, systemic vascular resistance was further reduced by the addition of nitroprusside to each dose of dopamine. Systemic vascular resistance was further reduced by 30 percent when nitroprusside was added to the small dose of dopamine ($P < 0.001$), 19 percent when combined with the intermediate dose ($P < 0.01$) and 31 percent when given with the large dose ($P < 0.01$). The combination of nitroprusside and dopamine further lowered systemic vascular resistance ($P < 0.01$) below the level obtained with nitroprusside alone.

Side effects of drug therapy: *Side effects of nitroprusside infusion* were relatively minor. Four patients complained of headache and three of nausea during nitroprusside-induced hypotension. One patient became diaphoretic, with a mean arterial pressure of 46 mm Hg. In contrast, four patients noted subjective improvement during nitroprusside therapy, with relief of dyspnea and diaphoresis. One patient, who had had hydralazine and prazosin discontinued 16 hours before, could not tolerate discontinuation of nitroprusside for more than 15 minutes without complaining of chest pain and dyspnea, associated with flushing and diaphoresis.

Side effects during intermediate and large dose infusions of dopamine were frequent and serious. In six patients the response to the 7 μg/kg per min dose of dopamine precluded them from receiving the larger dose. These side effects included frequent premature ventricular contractions (three patients), anginal chest pain (two patients), tachycardia of more than 130 beats/min (two patients), nausea with emesis (two patients), marked pulmonary systolic hypertension of more than 90 mm Hg (one patient) and arterial oxygen desaturation of less than 80 percent (one patient).

Of the seven patients who received the 15 μg/kg per min dose of dopamine, five had frequent premature ventricular contractions and five had tachycardia of at least 120 beats/min. In addition, five patients had an increase in pulmonary arterial wedge pressure to 38 mm

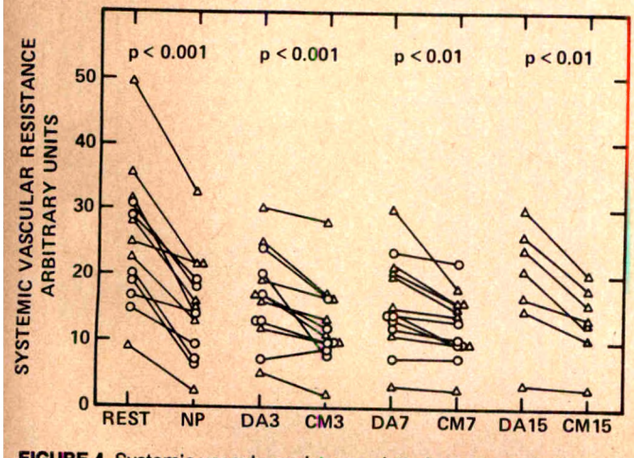

FIGURE 4. Systemic vascular resistance plotted at rest and during drug infusions. Resistance is significantly lower with nitroprusside than at rest, and with combination therapy than with dopamine alone at each dose. Abbreviations and symbols as in Figure 1.

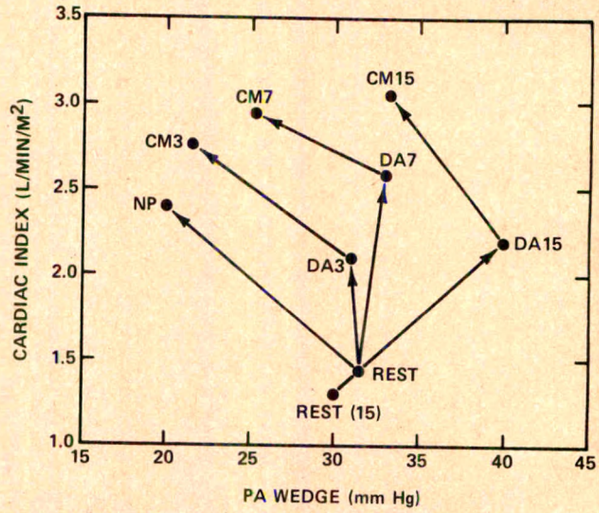

FIGURE 5. Mean left ventricular filling pressure, measured as pulmonary arterial (PA) wedge pressure plotted against mean cardiac index. The arrows show the change from the value at rest produced with nitroprusside (NP) and dopamine alone, and the change from the value with dopamine alone to that with combination therapy at each dose. Nitroprusside consistently increased cardiac index at a lower wedge pressure, whereas dopamine increased cardiac index with no change in wedge pressure at small (DA3) and intermediate doses (DA7), but with an increase in wedge pressure at the large dose (DA15). Rest (15) indicates the mean value at rest for the seven patients who received the large dose of dopamine alone and in combination with nitroprusside. Other abbreviations as in Figure 1.

Hg or greater. Only one patient, who had a resting heart rate of just 70 beats/min, tolerated the large dose of dopamine without hemodyanamic deterioration or ventricular arrhythmias.

Determinants of cardiac output: The effect of vasodilator and inotropic agents on cardiac output is a complex function of left ventricular preload, afterload, heart rate and contractility. Figure 5 plots the relation between pulmonary arterial wedge pressure and cardiac index during each drug infusion. There is no direct relation between pulmonary arterial wedge pressure and cardiac index, as would be predicted by a simple Starling mechanism with fixed impedance and left ventricular contractility. Thus the major effects of these drugs and drug combinations on cardiac output are not mediated by changes in preload.

Figure 6 plots the change in cardiac index as a function of the change in systemic vascular resistance. For each drug and drug combination, the change in cardiac output is proportional to the decrease in systemic vascular resistance. Thus, the effect of these drugs on cardiac output is mediated in large part by a change in systemic vascular resistance.

Figure 7 is a three-dimensional schematic illustration of the combined effects of preload, afterload and contractility on cardiac output. The illustration depicts a hypothetical three-dimensional left ventricular function plane at rest, which shows the change in cardiac index produced by changes in systemic vascular resistance and pulmonary arterial wedge pressure. When the contractile state of the left ventricle is altered, the plane of left ventricular function is elevated or lowered in three dimensions. This figure shows that in our patients, cardiac output was quite sensitive to changes in impedance and relatively insensitive to changes in left ventricular filling pressure, which explains the effectiveness of nitroprusside in improving circulatory function. When considered in this light, even the increase in cardiac output brought about by the intermediate dose of dopamine was due largely to decreased systemic vascular resistance rather than to increased left ventricular contractility.

Discussion

Our data provide, for the first time, a hemodynamic dose-response relation for dopamine alone and in combination with nitroprusside in patients with severe left ventricular failure. Previous studies of the dose-related hemodynamic response to dopamine in patients with congestive heart failure have been limited to moderate doses of dopamine. Ramdohr et al.[27] studied patients given dopamine infusions of 90, 195 and 350 μg/min and Beregovich et al.[19] gave doses of 1.5 and 10 μg/kg per min. These investigators found small increases in heart rate and blood pressure at the largest dose, with a small but insignificant increase in pulmonary wedge pressure. They also reported a dose-related increase of cardiac output with each additional dose.

We demonstrated a dose-related increase in cardiac output with dopamine until infusion rates of 15 μg/kg per min were reached, when peripheral arterial pressure began to increase. At this point the increase in afterload, compared with that at lower infusion rates, resulted in a less striking elevation of cardiac output. In addition,

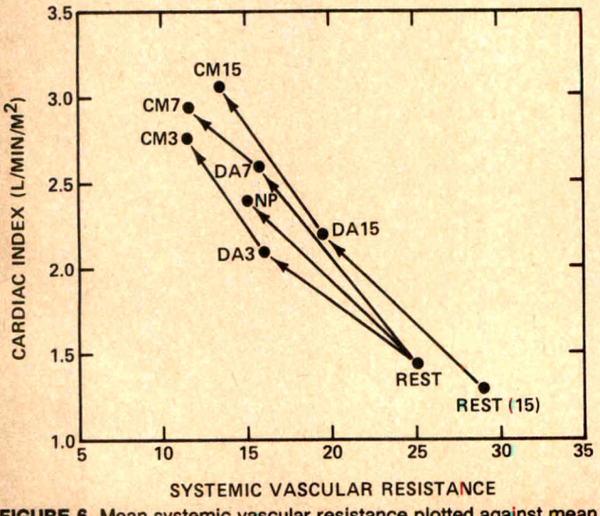

FIGURE 6. Mean systemic vascular resistance plotted against mean cardiac index. Changes in cardiac index from the resting state to single drug therapy and from dopamine to combination therapy are proportional to changes in vascular resistance; this finding is consistent with the small observed changes in mean arterial pressure. Abbreviations as in Figure 5.

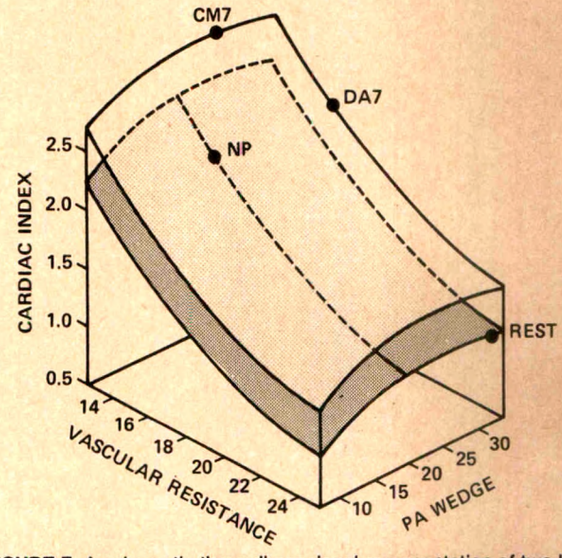

FIGURE 7. A schematic three-dimensional representation of two left ventricular function planes, each showing the cardiac index at various values of preload and afterload at a given inotropic state of the left ventricle. Experimental values at rest and with nitroprusside (NP) infusion are plotted on one plane; values with dopamine infusion at 7 μg/kg per min alone (DA7) and in combination with nitroprusside (CM7) are plotted on a second elevated plane, indicative of increased left ventricular contractility. The figure illustrates that in our patients cardiac index was more responsive to changes in afterload than to changes in preload or contractility. PA = pulmonary arterial.

there were increases in heart rate, pulmonary wedge pressure and, presumably, myocardial oxygen demands. Thus, we suggest that patients responding inadequately to higher infusion rates of dopamine might benefit substantially more from the addition of a vasodilator agent to their therapy than from a further increase in the rate of dopamine fusion.

After animal studies had demonstrated that alpha adrenergic blocking agents used in combination with dopamine resulted in greater augmentation of cardiac output and renal blood flow than that effected with dopamine alone,[28,29] case reports appeared describing the hemodynamic benefit of alpha adrenergic blocking agents used in patients with vasoconstriction who were unresponsive to dopamine alone.[16,30] Similarly, nitroprusside and dopamine together were reported to have resulted in hemodynamic and clinical improvement in two patients who did not respond to nitroprusside alone.[12]

Recently Miller et al.[31] studied the effect of combined dopamine-nitroprusside therapy in nine patients with mild to moderate left ventricular dysfunction. In their patients, combined therapy was more effective than nitroprusside alone in increasing cardiac output. However, dopamine at 6 μg/kg per min produced a comparable increment in output at a higher left ventricular end-diatolic pressure when compared with combination therapy. Our data extend these results to patients with severe left ventricular dysfunction and pulmonary congestion. In our patients, in contrast to those of Miller et al.,[31] there was a highly significant increment in cardiac output at all three dose levels of dopamine during combined vasodilator-catecholamine therapy over that achieved by dopamine alone.

Advantages of combination therapy: Combined nitroprusside-dopamine therapy offers at least three major advantages over dopamine alone in refractory congestive heart failure. First, for any given level of cardiac output, combination therapy results in a lower pulmonary wedge pressure and pulmonary arterial pressure than is achieved with dopamine alone, with a resultant improvement in pulmonary congestion. There is less metabolic demand on the left ventricle, both because of a decreased heart rate-systolic blood pressure product and because of a reduction in left ventricular diastolic volume, with its resultant decrease in wall tension. A smaller dose of dopamine, possible in combination therapy, also decreases the contractile state of the left ventricle and further reduces metabolic demand. Finally, a smaller dose of dopamine decreases the incidence of other side effects of dopamine, such as ventricular irritability and nausea, in addition to tachycardia and angina.

Combination therapy also offers advantages over nitroprusside therapy alone. There is a greater augmentation in cardiac output than is achieved with nitroprusside separately. Mean arterial blood pressure is maintained, thus assuming adequate renal, cerebral and coronary arterial perfusion, and allowing nitroprusside therapy of hypotensive patients.

Role of mitral regurgitation: The changes in pulmonary wedge pressure that we observed with both drugs may be due in part to changes in the degree of mitral regurgitation and resulting pulmonary wedge *V* wave, rather than solely to changes in vascular compliance and left ventricular functional state. Hemodynamic improvement during nitroprusside therapy has been previously reported in patients with mitral regurgitation.[32,33] However, the degree of improvement produced with nitroprusside and the degree of pulmonary wedge elevation during dopamine therapy were not consistently related to the degree of mitral regurgitation in each patient. These findings suggest that changes in the degree of mitral regurgitation associated with pharmacologic interventions were not major determinants of the beneficial effects of combined treatment we observed.

Other potential uses of combined therapy: Our study measured changes in cardiac output but did not investigate changes in regional blood flow. Thus the relative merits of combined versus single drug therapy in individual patients with myocardial ischemia, oliguria or altered mentation remain to be established. Nevertheless, the potential uses of combined nitroprusside-dopamine therapy are not limited solely to cases of refractory congestive heart failure. These drugs may also prove useful in managing patients with postoperative left ventricular failure, which is often associated with a high systemic vascular resistance. Pulmonary edema and cardiogenic shock should also be amenable to combination drug therapy in individual patients.

Therapeutic implications: Several clinical conclusions are suggested by these studies. First, although the approach to any patient with left ventricular dysfunction depends upon the specific clinical setting, for best management in critical cases an arterial line and Swan-Ganz thermodilution catheter should be inserted to allow determination of preload, afterload and cardiac output. Second, in many patients with left ventricular dysfunction and an elevated left ventricular filling pressure, nitroprusside therapy alone will prove adequate. Third, if inadequate cardiac output persists, the addition of dopamine to nitroprusside should result in further hemodynamic improvement. Finally, the patient may be given oral medication such as hydralazine and isosorbide dinitrate, and the hemodynamic effect can be directly measured.

We have demonstrated that the combination of vasodilator and inotropic therapy with nitroprusside and dopamine results in hemodynamic improvement not attainable with either drug alone. Major disadvantages of the individual agents are avoided, and cardiac output is increased over the level achieved with any dose of either drug. We conclude that combined dopamine and nitroprusside therapy provides an excellent method of reversing refractory congestive heart failure in appropriately selected patients.

Acknowledgment

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References

1. **Chatterjee K, Parmley W:** The role of vasodilator therapy in heart failure. Prog Cardiovasc Dis 19:301–325, 1977
2. **Cohn JN:** Vasodilator therapy for heart failure. The influence of impedance on left ventricular performance. Circulation 47:5–8, 1973
3. **Chatterjee K:** Vasodilator therapy for heart failure. Ann Intern Med 83:421–423, 1975
4. **Gulha NH, Cohn JN, Mikulic E:** Treatment of refractory heart failure with infusion of nitroprusside. N Engl J Med 291:586–592, 1974
5. **Chatterjee K, Parmley WW, Ganz W:** Hemodynamic and metabolic responses to vasodilator therapy in acute myocardial infarction. Circulation 48: 1183–1193, 1973
6. **Majid PA, Sharma B, Taylor SH:** Phentolamine for vasodilator treatment of severe heart failure. Lancet 2:719–723, 1971
7. **Mikulic E, Franciosa JA, Cohn JN:** Comparative hemodynamic effects of chewable isosorbide dinitrate and nitroglycerin in patients with congestive heart failure. Circulation 52:477–482, 1975
8. **Gold HK, Leinbach RC, Sanders CA:** Use of sublingual nitroglycerin in congestive heart failure following acute myocardial infarction. Circulation 46:839–845, 1972
9. **Armstrong PW, Walker DC, Burton JR:** Vasodilator therapy in acute myocardial infarction. A comparison of sodium nitroprusside and nitroglycerin. Circulation 52:1118–1122, 1975
10. **Williams DO, Amsterdam EA, Mason DT:** Hemodynamic effects of nitroglycerin in acute myocardial infarction. Decrease in ventricular preload at the expense of cardiac output. Circulation 51: 421–427, 1975
11. **Meister SG, Furr C, Gilson F, et al:** Sustained hemodynamic effects of nitroglycerin ointment (abstr). Am J Cardiol 37:155, 1976
12. **Franciosa JA, Mikulic E, Cohn JN, et al:** Hemodynamic effects of orally administered isosorbide dinitrate in patients with congestive heart failure. Circulation 50:1020–1027, 1974
13. **Kovick RB, Tillisch JH, Berens SC, et al:** Vasodilator therapy for chronic left ventricular failure. Circulation 53:322–328, 1976
14. **Chatterjee K, Parmley WW, Massie B, et al:** Oral hydralazine therapy for chronic refractory heart failure. Circulation 54:879–883, 1976
15. **Franciosa J, Pierpont G, Cohn J:** Hemodynamic improvement after oral hydralazine in left ventricular failure. Ann Intern Med 86: 388–393, 1977
16. **Goldberg LI:** Use of sympathomimetic amines in heart failure. Am J Cardiol 22:177–182, 1968
17. **Goldberg LI:** Drug therapy: dopamine—clinical uses of an endogenous catecholamine. N Engl J Med 291:707–710, 1974
18. **Goldberg L, Hsien Y, Resnekov L:** Newer catecholamines for treatment of heart failure and shock. An update on dopamine and a first look at dobutamine. Prog Cardiovasc Dis 19:327–340, 1977
19. **Beregovich J, Bianchi C, Rubler S, et al:** Dose-related hemodynamic and renal effects of dopamine in congestive heart failure. Am Heart J 87: 550–557, 1974
20. **Goldberg L:** Cardiovascular and renal actions of dopamine: potential clinical applications. Pharmacol Rev 24:1–29, 1972
21. **daLuz PL, Forrester JS, Wyatt HL, et al:** Hemodynamic and metabolic effects of sodium nitroprusside on the performance and metabolism of regional ischemic myocardium. Circulation 52: 400–407, 1975
22. **Mueller H, Religa A, Evans R, et al:** Metabolic changes in ischemic myocardium by nitroprusside (abstr). Am J Cardiol 33:158, 1974
23. **Shell WE, Sobel BE:** Protection of jeopardized ischemic myocardium by reduction of ventricular afterload. N Engl J Med 291: 481–486, 1974
24. **Reid PR, Pitt B, Kelly DT:** Effects of dopamine on increasing infarct area in acute myocardial infarction (abstr). Circulation 46:Suppl II:II-210, 1972
25. **Crexells C, Bourassa M, Birou P:** Effects of dopamine on myocardial metabolism in patients with ischemic heart disease. Cardiovasc Res 7:438–445, 1973
26. Criteria Committee of the New York Heart Association: Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels, seventh edition. Boston, Little, Brown, 1973, p 286
27. **Ramdohr B, Schuren KP, Biamini G, et al:** Der Einfluss von Dopamin auf Hamodynamik und Nierenfunktion bei der schweren Herzinsuffizienz des Menschen. Klin Wochenschr 51:549–556, 1973
28. **McNay JL, Goldberg LI:** Comparison of the effects of dopamine, isoproterenol, norepinephrine and bradykinin on canine renal and femoral blood flow. J Pharmacol Exp Ther 151:23–31, 1966
29. **Bagwell EE, Daniell HB, Freeman BF:** Influence of phentolamine on the cardiovascular effects of dopamine in experimental cardiogenic shock. Arch Int Pharmacodyn Ther 208:197–203, 1974
30. **MacCannell KL, McNay JL, Meyer MB, et al:** The use of dopamine in the treatment of hypotension and shock. N Engl J Med 275: 1389–1398, 1966
31. **Miller RR, Awan NA, Joye JA, et al:** Combined dopamine and nitroprusside therapy in congestive heart failure. Greater augmentation of cardiac performance by addition of inotropic stimulation to afterload reduction. Circulation 55:881–884, 1977
32. **Chatterjee K, Parmley WW, Swan HJC, et al:** Beneficial effects of vasodilator agents in severe mitral regurgitation due to dysfunction of subvalvular apparatus. Circulation 48:684–690, 1973
33. **Goodman DJ, Rossen RM, Holloway EL, et al:** Effect of nitroprusside on left ventricular dynamics in mitral regurgitation. Circulation 50:1025–1032, 1974

Human Electropharmacology of Tocainide, a Lidocaine Congener

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The electropharmacology of tocainide, an orally active congener of lidocaine, was evaluated in 10 patients with coronary artery disease. Electrophysiologic measurements including sinus nodal recovery time, sinoatrial conduction time, intraatrial conduction time, atrial, atrioventricular (A-V) nodal and ventricular refractory periods and intraventricular conduction time were obtained before and after intravenous infusion of tocainide. At blood levels shown to be effective against ventricular arrhythmias, tocainide produced no statistically significant changes in the electrophysiologic measurements, although occasional marked individual effects were observed. No side effects were observed during these studies. No adverse effects on A-V conduction were observed in patients with an intraventricular conduction disturbance or a prolonged control H-V interval. Thus, plasma tocainide concentrations effective in the therapy of ventricular arrhythmias exert no adverse effects on cardiac electrophysiologic properties in patients with coronary artery disease.

Tocainide, a congener of lidocaine, is an effective antiarrhythmic agent that is active orally.[1,2] Although studies of tocainide in isolated preparations and animal models suggest that it is electrophysiologically similar to lidocaine,[1,3] the effects of tocainide on human cardiac electrophysiology have not been reported. This study was undertaken to evaluate comprehensively the electropharmacology of tocainide in human subjects with coronary artery disease.

Material and Methods

Subjects: Ten patients with coronary artery disease were studied after informed consent was obtained (Table I). Coronary artery disease was diagnosed on the basis of a history of documented myocardial infarction (four patients), angiographically demonstrated coronary artery disease (greater than 70 percent luminal narrowing of at least one coronary vessel) (five patients) or classic angina pectoris (five patients). Five patients had ventricular arrhythmias, and four had an intraventricular conduction disturbance. Each patient was undergoing routine electrophysiologic study for clinical symptoms. No cardiac angiographic studies were performed within 24 hours of the tocainide studies. The protocol was approved by the University Committee on the Use of Human Subjects.

Electrophysiologic procedures: Right heart catheterization was performed with patients in the nonsedated postabsorptive state. Antiarrhythmic drugs were withheld for 48 hours before the study. Quadripolar electrode catheters were introduced percutaneously and positioned under fluoroscopic control in the right atrium (RA), coronary sinus (CS) and right ventricular apex (RVA). In two patients an additional catheter was positioned in the left ventricle. Bipolar electrograms were recorded with the proximal electrodes, and stimulation was performed through the distal electrode pair. A His bundle electrogram was obtained by positioning a tripolar electrode catheter across the tricuspid valve. The intracardiac electrograms were filtered at 40 to 500 hertz and simultaneously displayed with three surface electrocardiographic leads (I, aVF and V_1) and time

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TABLE I

Clinical Data

Case no.	Age (yr) & Sex	ECG	Documentation of CAD
1	62M	NS ST-T	Angina pectoris
2	56F	RBBB, LAHB	Angina pectoris
3	52M	NS ST-T	Angina pectoris, MI
4	59M	1° AVB, IMI	Angina pectoris, MI
5	51M	Normal	Coronary angiography
6	50F	RBBB, LAHB	Angina pectoris
7	46M	Normal	Coronary angiography
8	52M	LBBB	Coronary angiography, MI
9	57M	LIVCD	Coronary angiography
10	47M	AMI	Coronary angiography, MI

AMI = anterior myocardial infarction; CAD = coronary artery disease; ECG = electrocardiogram; IMI = inferior myocardial infarction; LAHB = left anterior hemiblock; LBBB = left bundle branch block; LIVCD = intraventricular conduction defect, left bundle branch block type; MI = documented myocardial infarction; NS ST-T = nonspecific ST-T wave abnormalities; 1° AVB = first degree A-V block; RBBB = right bundle branch block.

TABLE II

Plasma Tocainide Concentrations (μg/ml)

Case no.	T_0	T_{15}	Infusion Rate (mg/kg per min)
1	1.3	1.2	0.5
2	2.5	2.9	0.5
3	1.6	2.0	0.5
4	2.0	1.7	0.5
5	5.8	4.9	0.75
6	6.1	5.6	1.0
7	14.3	11.4	1.0
8	12.4	5.9	1.0
9	10.8	7.9	1.0
10	16.9	5.6	1.0

T_0 = end of tocainide infusion; T_{15} = 15 minutes after end of tocainide infusion.

lines generated at 10 and 100 msec on a multichannel oscilloscope (Electronics for Medicine, DR-16). Data were stored on magnetic tape (Honeywell 5600C) and retrieved on photographic paper at speeds of 100 to 200 mm/sec.

Measurements: Programmed stimulation was performed with a custom-designed digital stimulator with isolated constant current sources. Stimuli were 1 msec in duration and twice diastolic threshold. Electrophysiologic measurements were made of sinus nodal and corrected sinus nodal recovery times[4,5]; sinoatrial[6] and intraatrial[7] conduction times; atrial,[8] anterograde atrioventricular (A-V) nodal[8] and ventricular effective refractory periods[9]; His-Purkinje system relative refractory period[10]; and intraventricular conduction time (measured from the onset of ventricular activation [Q] in the surface electrocardiogram to the right ventricular apical electrogram [Q-RV interval] and the left ventricular electrogram recorded in the coronary sinus[11] or directly from the left ventricular cavity [Q-LV]). All refractory periods were measured at a paced cycle length of 600 msec. Conduction intervals were measured during sinus rhythm and atrial pacing at a cycle length of 600 msec. Measurements of conduction times were made at the point at which the first rapid deflection of the respective electrograms crossed the baseline. Sinus cycle length, P-R interval, QRS duration and Q-T interval were measured in simultaneously recorded leads I, aVF and V_1 at a paper speed of 200 mm/sec. The corrected Q-T interval (Q-Tc) was calculated from these data.

Tocainide infusion: After control measurements were obtained, tocainide was infused by an Imed pump at doses of 0.5, 0.75 or 1.0 mg/kg per min for 15 minutes. Only one dose was used in each patient. Venous blood samples for determination of tocainide plasma cconcentration[1] were obtained before and 1, 5, 10, 15, 20, 45, 75 and 195 minutes after the start of the infusion. Blood pressure was measured with a

TABLE III

Electrocardiographic Intervals† and Blood Pressure Response to Tocainide Infusion

Case	P-R			QRS			Q-T			Q-Tc			BP (mm Hg)		
no.	C	T_0	T_{15}	C	T_0	T_{15}	C	T_0	T_{15}	C	T_0	T_{15}	C	T_0	T_{15}
1	160	155	158	100	100	102	400	370	380	454	416	432	116/68	126/70	120/65
2	162	160	162	124	120	120	372	360	354	459	444	437	120/70	125/72	115/70
3	182	172	180	100	100	100	422	402	410	502	462	471	140/90	136/90	145/95
4	290	278	272	98	100	100	420	410	428	416	410	420	180/90	170/90	170/95
5	182	196	200	112	109	106	372	364	354	423	418	402	160/85	180/85	160/80
6	140	162	160	122	124	120	430	410	400	483	461	454	140/80	136/80	136/80
7	192	190	192	85	85	85	320	312	310	381	371	364	130/95	135/90	140/90
8	202	200	200	142	144	140	330	330	330	402	402	400	115/70	120/75	120/70
9	196	194	196	120	120	124	320	322	320	381	398	390	135/70	130/75	135/75
10	122	120	120	80	82	80	338	350	350	349	391	391	110/70	115/75	115/70
Mean ±SD	183 ±45	183 ±41*	184 ±40*	108 ±19	109 ±19*	98 ±36*	372 ±44	363 ±36*	363 ±40*	425 ±49	417 ±49*	416 ±33*			

* No significant change from control measurements.
† All interval measurements in milliseconds.
BP = blood pressure; C = control; SD = standard deviation; T_0 = end of tocainide infusion; T_{15} = 15 minutes after end of tocainide infusion.

TABLE IV

Sinus Nodal Function Before and After Tocainide*

Case no.	Sinus Cycle Length			SNRT/CSNRT			Sinoatrial Conduction Time (normal <150 msec)		
	C	T_0	T_{15}	C	T_0	T_{15}	C	T_0	T_{15}
1	775	800	775	1200/425	1100/300	1200/425	150	105	90
2	650	650	650	1050/400	1020/570	970/330	110	100	100
3	700	750	750	1040/340	1090/340	1000/250	75	60	55
4	1020	1000	1050	1600/580	1620/620	1580/530	190	170	165
5	780	750	780	1280/500	1200/450	1240/460	210	85	150
6	800	800	770	1150/350	1150/300	1120/380	100	120	160
7	700	700	720	1200/500	1150/450	1200/480	115	65	45
8	680	680	670	880/200	1100/420	950/280	105	85	85
9	700	680	680	950/250	920/260	920/290	100	105	100
10	960	760	760	1200/240	1030/270	1100/340	115	125	165
Mean	776	755	760	1155 ± 200/	1138 ± 187†/	1128 ± 196†/	127	102	111
±SD	±123	±101†	±112†	378 ± 126	398 ± 126†	371 ± 100†	± 43	± 32†	± 45†

* All measurements in milliseconds.
† No significant change from control measurements.
C = control; CSNRT = corrected sinus nodal recovery time (normal less than 550 msec); SACT = sinoatrial conduction time (normal less than 150 msec); SD = standard deviation; SNRT = sinus nodal recovery time (normal less than 150 percent of sinus cycle length or less than 2,000 msec); T_0 = end of tocainide infusion; T_{15} = 15 minutes after end of tocainide infusion.

TABLE V

Refractory Periods Before and After Tocainide Infusion

Case no.	A-ERP			AVN-ERP			HPS-RP			RV-ERP		
	C	T_0	T_{15}	C	T_0	T_{15}	C	T_0	T_{15}	C	T_0	T_{15}
1	300	240	240	...	...	...	440	380	380	240	240	250
2	210	200	210	250	270	260	...	...	...	210	210	210
3	320	280	280	530	950	450	625	520	520	250	250	250
4	260	280	250	390	380	400	...	...	...	240	250	250
5	250	240	250	290	260	270	450	425	425	210	220	220
6	210	200	200	210	220	200	...	...	...	210	200	200
7	230	220	210	370	330	350	...	...	...	190	190	190
8	260	260	250	...	...	...	...	...	...	240	240	240
9	220	220	220	320	300	290	...	...	...	210	180	200
10	250	260	210	300	280	260	...	...	...	260	260	260
Mean	251	240	232	332	311	310	505	441	441	226	224	227
±SD	±37	±30*	±26*	±99	±74*	±33*	±104	±71*	±71*	±23	±28*	±26*

* No significant change from control measurements.
A-ERP = atrial effective refractory period (normal 170 to 300 msec); AVN-ERP = A-V nodal effective refractory period (normal 230 to 425 msec); HPS-RP = His-Purkinje system relative refractory period (normal 330 to 450 msec); RV-ERP = right ventricular effective refractory period (normal 170 to 290 msec); SD = standard deviation.

TABLE VI

Intracardiac Conduction Times (msec)

Case no.	P-HRA			P-MRA			P-LRA			P-HBE		
	C	T_0	T_{15}	C	T_0	T_{15}	C	T_0	T_{15}	C	T_0	T_{15}
1	26	31	30	42	42	44	57	60	64	65	65	65
2	10	10	10	30	32	32	54	50	50	30	30	30
3	35	32	30	10	15	12	63	59	60	60	62	62
4	40	30	30	5	0	5	50	52	52	48	45	45
5	10	12	10	30	32	30	62	64	64	50	52	50
6	20	20	20	29	32	35	62	65	65	40	40	40
7	22	22	21	30	30	30	52	52	52	70	70	70
8	20	20	20	12	10	12	85	82	84	40	40	35
9	38	38	23	60	50	45	50	50	50	65	62	60
10	0	0	0	18	18	15	30	35	38	30	30	30
Mean	22	22	19	27	26	26	57	57	58	50	50	49
±SD	±13	±12*	±10*	±16	±15*	±14*	±14	±12*	±15*	±15	±15*	±15*

* No significant change from control measurements.
A-H = A-H interval of His bundle electrogram measured during sinus rhythm (normal 70 to 150 msec) (values in parentheses are A-H intervals measured during high right atrial pacing at a cycle length of 600 msec); C = control; H-V = H-V interval of His bundle electrogram measured during sinus rhythm (normal 35 to 55 msec); P-HBE = onset of P wave to atrial electrogram in the His bundle electrogram (normal 43 ± 8 msec); P-HRA

sphygmomanometer at the time of each blood sample. The electrophysiologic measurements were repeated at the end of the infusion (T_0) and 15 minutes (T_{15}) after the end of the infusion. The statistical data were analyzed using Student's paired *t* test.

Results

The infusion of tocainide was accomplished at all dose levels without side effects. The tocainide blood levels at which the electrophysiologic measurements were made are indicated in Table II. Tocainide caused no significant change in heart rate, blood pressure, P-R interval, QRS duration or Q-T (Q-Tc) interval (Table III).

There were no statistically significant alterations in any electrophysiologic measurement during these studies. Furthermore, no significant effects were observed specifically in patients attaining the highest plasma tocainide concentrations.

Sinus node: The sinus nodal and corrected sinus nodal recovery times were not significantly changed by tocainide (Table IV). Although in three patients (Patients 1, 3 and 7) the recovery time decreased, the difference was not statistically significant for the entire group. No patient had abnormal sinus function during control measurements.

Atrium: The effective refractory period of the atrium (A-ERP) was not significantly changed by tocainide (Table V). However, in three patients marked shortening of this period (40 to 60 msec) was observed. The change in these patients could not be explained by differences in control measurements or the effects of other drugs such as digitalis. Similarly, intraatrial conduction was not affected by tocainide (Table VI).

A-V node: Neither the A-H interval measured during sinus rhythm or at a paced atrial cycle length of 600 msec nor the pacing cycle length at which type I (Wenckebach) A-V nodal block occurred was altered by tocainide (Table VI). The effective refractory period of the A-V node could be measured in eight patients (Table V). In the two remaining patients, the effective refractory period of the atrium was reached before that of the A-V node could be determined. The effects on A-V nodal refractoriness were variable. In the patient with the longest effective refractory period of the A-V node (Patient 3), tocainide caused a marked reduction of refractoriness (80 msec), but in two patients (Patients 2 and 4) there was a minimal increase. No significant change was observed for the group.

His-Purkinje system: There were no changes in the H-V interval after tocainide infusion, even in the patients whose control H-V interval was prolonged (Patients 1, 2, 6 and 8) or in the patients who had bifascicular block (right bundle branch block/left anterior hemiblock) or left bundle branch block (Table VI). His-Purkinje refractoriness could be measured in three patients and showed a modest but not statistically significant decrease.

Ventricle: Tocainide produced no significant change in the effective refractory period of the right ventricle (Table V).

Discussion

Since its introduction as an antiarrhythmic agent in 1950,[13] lidocaine has become the agent of choice in the acute management of ventricular arrhythmias and the prevention of ventricular fibrillation during acute myocardial infarction.[12] However, the use of lidocaine has been restricted by the lack of an oral preparation. In this report we have presented the clinical electrophysiologic effects of tocainide, a lidocaine congener that is orally effective. Our studies were performed after intravenous administration of tocainide because this method assured predictable blood levels and avoided the delay required for absorption after oral administration.

Comparison of tocainide and lidocaine: Like lidocaine,[10,14–17] tocainide exerts no significant effect on sinus nodal function or atrial, A-V nodal or ventricular

TABLE VI continued

Case no.	P-LA/CS			A-H			H-V			Q-RV			Q-LV		
	C	T_0	T_{15}	C	T_0	T_{15}	C	T_0	T_{15}	C	T_0	T_{15}	C	T_0	T_{15}
1	80	90	90	65(70)	62(65)	65(68)	62	60	60	28	30	25	38	40	45
2	...	...	...	70(100)	70(92)	70(95)	52	52	52	38	38	38	...	...	...
3	102	102	103	80(110)	80(105)	80(105)	55	55	56	30	30	29	70	70	71
4	...	...	...	165(190)	150(180)	155(185)	50	50	50	0	0	0	...	...	...
5	100	100	100	105(120)	100(115)	180(120)	55	55	55	40	40	40	63	61	63
6	80	80	80	80(90)	80(90)	80(90)	50	50	50	20	10	20	30	20	30
7	...	...	...	100(140)	100(138)	100(140)	52	52	52	26	26	26	...	...	...
8	...	...	...	90(85)	100(80)	90(83)	55	55	55	5	5	5	65	65	55
9	78	75	70	100(110)	100(115)	100(115)	50	50	50	20	20	20	30	30	30
10	...	...	...	65(80)	65(70)	65(72)	50	50	50	12	15	18	18	20	22
Mean ±SD	88 ±12	89 ±12*	89 ±14*	92 ± 30 (109± 35)	91 ± 26* (105 ± 35)*	99 ± 39* (107 ± 35)*	54 ± 4	52 ± 3*	53 ± 3*	22 ±13	21 ± 14*	22 ± 13*	45 ± 21	44 ± 21*	45 ± 19*

= onset of P wave to high right atrial electrogram (normal 15 ± 11 msec); P-LA/CS = onset of P wave to left atrial/coronary sinus atrial electrogram (normal 77 ± 8 msec); P-LRA = onset of P wave to low right atrial electrogram (normal 41 ± 13 msec); P-MRA = onset of P wave to mid right atrial electrogram (normal 12 ± 9 msec); Q-LV = Q wave to left ventricular electrogram measured during sinus rhythm (normal 41 ± 15 msec); Q-RV = Q wave to right ventricular electrogram measured during sinus rhythm (normal 18 ± 9 msec); SD = standard deviation; T_0 = end of tocainide infusion; T_{15} = 15 minutes after end of tocainide infusion.

refractory periods. Some patients, however, have marked changes in these functions. Similar marked individual changes in refractory periods have been noted after administration of lidocaine.[10]

One of the most important features of lidocaine is its favorable therapeutic/toxicity ratio. Effective levels of the drug are associated with few clinical side effects and little adverse effect on A-V conduction. However, infra-His conduction disturbances have been attributed to lidocaine administered in the presence of a diseased A-V conduction system.[7,16,18] Although in experimental studies tocainide in toxic doses caused prolongation of both A-H and H-V intervals and ventricular activation time,[3] in our patients with and without preexisting intraventricular conduction defects, tocainide produced no changes in infra-His or intraventricular conduction during basal conditions or during anterograde stress of the conduction system. The plasma tocainide levels in our patients (1.3 to 16.9 μg/ml) were within the therapeutic range, and we were unable to document any adverse effects on A-V conduction when tocainide was administered at appropriate plasma concentrations. However, because lidocaine toxicity of this type often occurs during high plasma concentrations,[15] it is possible that tocainide may cause similar toxic effects at plasma levels above the therapeutic range.

Clinical implications: The antiarrhythmic efficacy of tocainide was recently investigated by Winkle et al.[2] Their study showed that tocainide in plasma concentrations of 5 to 18 μg/ml effectively suppressed a variety of ventricular arrhythmias. In our study, similar plasma tocainide concentrations effective in the treatment of ventricular arrhythmias without clinical toxicity exerted no adverse effects on cardiac electrophysiologic properties in patients with coronary artery disease, a group in which tocainide may be especially useful.

It is not surprising that tocainide has little effect on clinical electrophysiologic properties although it is effective against ventricular arrhythmias. Tocainide's ability to depress the slope of phase 4 depolarization and hence suppress enhanced automaticity cannot be assessed from clinical electrophysiologic studies. Moore et al.[3] demonstrated that tocainide possesses this ability in vitro and in vivo. Furthermore, lidocaine, which has potent antiarrhythmic effects, similarly produces minimal clinical electrophysiologic changes. The effects of tocainide and lidocaine may be exerted through alterations of membrane responsiveness and local conduction and refractoriness; these alterations cannot be assessed with electrophysiologic testing in man.

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References

1. **Coltart DJ, Berndt TB, Kernoff R, et al:** Antiarrhythmic and circulatory effects of Astra W36095. A new lidocaine-like agent. Am J Cardiol 34:35–41, 1974
2. **Winkle RA, Mifflin PJ, Fitzgerald JW, et al:** Clinical efficacy and pharmacokinetics of a new orally effective antiarrhythmic, tocainide. Circulation 54:884–889, 1976
3. **Moore EN, Spear JF, Horowitz LN, et al:** Electrophysiologic properties of a new antiarrhythmic drug—tocainide. Am J Cardiol 41:703–709, 1978
4. **Mandel W, Hayakawa H, Danzig R, et al:** Evaluation of sino-atrial node function in man by overdrive suppression. Circulation 44: 59–65, 1971
5. **Narula OS, Samet P, Javier RP:** Significance of the sinus-node recovery time. Circulation 45:140–158, 1972
6. **Strauss HC, Saroff AL, Bigger JT, et al:** Premature atrial stimulation as a key to the understanding of sinoatrial conduction in man. Circulation 47:86–93, 1973
7. **Josephson ME, Scharf DL, Kastor JA, et al:** Atrial endocardial activation in man. Electrode catheter technique for endocardial mapping. Am J Cardiol 39:972–981, 1977
8. **Denes P, Wu D, Dhingra R, et al:** The effects of cycle length on cardiac refractory periods in man. Circulation 49:32–41, 1974
9. **Guss SB, Kastor JA, Josephson ME, et al:** Human ventricular refractoriness. Effects of cycle length, pacing site and atropine. Circulation 53:450–455, 1976
10. **Josephson ME, Caracta AR, Lau SH, et al:** Effects of lidocaine on refractory periods in man. Am Heart J 84:778–786, 1972
11. **Kastor JA, Goldreyer BN, Moore EN, et al:** Intraventricular conduction in man studied with an endocardial electrode catheter mapping technique. Circulation 51:786–796, 1975
12. **Lie KI, Wellens HJ, VanCapelle FJ, et al:** Lidocaine in the prevention of primary ventricular fibrillation. N Engl J Med 291: 1324–1326, 1974
13. **Southworth JL, McKusick VA, Peirce EC, et al:** Ventricular fibrillation precipitated by cardiac catheterization; complete recovery of patient after 45 minutes. JAMA 143:717–720, 1950
14. **Rosen KM, Lay SH, Weiss MB:** The effect of lidocaine on atrioventricular conduction in man. Am J Cardiol 25:1–5, 1970
15. **Collinsworth KA, Kolman S, Harrison DC:** The clinical pharmacology of lidocaine as an antiarrhythmic drug. Circulation 50: 1217–1230, 1974
16. **Rosen MR, Hoffman BF, Wit AL:** Electrophysiology and pharmacology of cardiac arrhythmias. V. Cardiac antiarrhythmic effects of lidocaine. Am Heart J 89:526–536, 1975
17. **Ross JC, Dunning AJ:** Effects of lidocaine on impulse formation and conduction defects in man. Am Heart J 89:686–699, 1975
18. **Engel TR, Soly KL, Meister SG, et al:** Effect of lidocaine on right ventricular muscle refractoriness. Clin Pharmacol Ther 19: 515–522, 1976
19. **Gupta PK, Lichstein E, Chadda KD:** Lidocaine-induced heart block in patients with bundle branch block. Am J Cardiol 33:487–492, 1974

Recurrent Cardiac Tamponade and Large Pericardial Effusions: Management With an Indwelling Pericardial Catheter

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A new technique, using an atraumatic indwelling catheter, has been developed for short-term management of large or rapidly reaccumulating pericardial effusions. This technique (1) permits continuous pericardial fluid drainage, obviating repeated aspirations; (2) provides a convenient route for intrapericardial instillation of chemotherapeutic agents; and (3) enables one to await the results of diagnostic studies without subjecting a patient to thoracotomy. Experience in three patients suggests that in some cases the use of this catheter may eliminate the need for surgery; in others, it may serve as a valuable temporary measure to achieve stabilization of the patient's condition.

Although successful pericardial aspiration was performed as early as 1840,[1] the importance of pericardiocentesis for diagnostic and therapeutic purposes has become widely recognized only in the past 40 years. It is usually undertaken with some trepidation because of potential complications, including arrhythmias, cardiac perforation and coronary arterial laceration. Occasionally recurrent cardiac tamponade or a large pericardial effusion requires repeated pericardiocentesis and the consideration of open drainage or pericardiectomy. However, in very ill patients, repeated aspirations or surgical procedures requiring general anesthesia easily lead to morbidity. We describe a safe and simple technique for insertion of a soft large-bore curved radiopaque catheter containing multiple side holes that permits prolonged pericardial fluid drainage and makes possible intrapericardial instillation of chemotherapeutic agents. The technique is especially useful in patients with hemorrhagic or suppurative effusions in which the fluid is viscous or prone to clotting as in cases of malignant, purulent or uremic pericarditis.

Methods and Results

This procedure has been performed recently in three patients who had a large pericardial effusion with recurrent cardiac tamponade. The clinical information and results of pericardiocentesis are summarized in Table I.

After the extent of the pericardial effusion was documented with echocardiography, pericardiocentesis was performed in the intensive care unit under sterile conditions using standard techniques.[2] The xiphisternal route is preferred because it avoids the pleura and major coronary vessels. After the skin and subcutaneous tissues were anesthetized, a thin-walled no. 18 Seldinger needle, directly monitored by attachment to the precordial lead of a well grounded electrocardiograph,[3] was introduced just below the xiphoid process. The needle was slowly advanced until the pericardial space was entered or until S-T segment elevation or ventricular extrasystoles appeared in the monitoring electrocardiogram. When the pericardial space was entered and the needle tip lay freely in the pericardial fluid, the stylette was removed and samples of fluid were aspirated for chemical, bacteriologic, cytologic and immunologic examination. A Teflon®-coated spring guide wire with a flexible tip (Argon Medical Corporation, no. 395321) was passed through the needle, which was then withdrawn. A no. 8F vessel dilator (Cordis no. 501-200) was then introduced over the guide wire,

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TABLE I

Clinical Data and Results of Periocardiocentesis

Case no.	Diagnosis	Prior Radio-/ Chemo-Therapy	no. of Periocardio-centeses	Indwelling Catheter Time	Total Fluid Removed (ml)	Pericardial Fluid Cytologic Study	Other Treatment	Duration of Effusion Control
1	Metastatic breast carcinoma	No/Yes	2	2 days	890	Positive	800 rads, pericardium	6 mo.
2	Metastatic lung carcinoma	Yes/No	3	8 days	3150	Positive	60 u Bleomycin, pericardial space	14 days
3	Metastatic lung carcinoma	Yes/No	3	6 days	2650	Positive	60 u Bleomycin, pericardial space	2.5 mo.

thus enlarging the tract into the pericardial space. A no. 8F polyurethane femoral-ventricular "pigtail" catheter with 12 side holes and 1 end hole (Cordis no. 523-850), cut short and fitted with a hub adaptor, was passed into the pericardium over the guide wire. Fluoroscopy permitted placement of the catheter in a dependent portion of the pericardial space for optimal drainage of fluid. The catheter was attached by means of a three way stopcock and connecting tubing to a closed sterile container with vacuum drainage. The catheter was flushed aseptically every hour with 2 to 3 cc of heparinized saline solution, and the amount of drainage was recorded. To facilitate evacuation of the pericardial fluid, the patient's position was periodically changed from side to side, upright and supine.

Asepsis was maintained during insertion of the catheter and while it remained in place. The point of entrance of the catheter hub and adaptor required careful sterile dressing, and any manipulation or flushing was performed aseptically.

Discussion

Insertion of an intrapericardial catheter avoids the need to have a rigid needle in the pericardial space for a prolonged period of time or to perform repeated aspirations in cases of large or rapidly reaccumulating pericardial effusions. The catheter system described here is superior to small-bore tubing inserted through the aspiration needle because this catheter is larger and the multiple side holes make occlusion by viscous or hemorrhagic fluid less likely.[4,5] In addition, the curved end of the "pigtail" catheter is less likely than the blunt tip of a straight catheter to lacerate epicardial coronary vessels. In our experience, this curved catheter has not provoked cardiac arrhythmias by contact with the heart. If necessary, the catheter can be changed with ease, and in one case when satisfactory drainage ceased after 72 hours, a guide wire was reintroduced, the catheter withdrawn and a new catheter inserted for an additional 5 days.

Clinical applications: An indwelling catheter in the pericardial space permits one to await the results of diagnostic studies such as cytology without subjecting a patient to general anesthesia and thoracotomy. In Patient 1, who had metastatic breast carcinoma, the diagnosis of malignant pericardial effusion was made from cells aspirated from the pericardial space and the recurring tamponade was controlled while radiotherapy was initiated. After administration of 800 rads to the pericardium, the pericardial drainage ceased and the catheter was removed. There was no recurrence of tamponade or clinically apparent effusion during a 6 month follow-up period.

In addition, antineoplastic, antiinflammatory or antibiotic agents can be instilled through this indwelling catheter. In Patient 3, for example, pericardial lavage with a Bleomycin solution was performed during a 6 day period, after which the catheter was removed without recurrence of the effusion.

This procedure may be useful in patients with hemorrhagic uremic pericarditis and recurrent tamponade,[6,7] malignant pericardial effusion[8,9] or purulent pericarditis and a large pericardial effusion. It may also be applicable in patients with traumatic hemopericardium or with hemorrhagic pericarditis secondary to postmyocardial infarction syndrome. In some patients, the procedure may make pericardiotomy or pericardiectomy unnecessary or entirely eliminate the need for surgery; in others, such as critically ill patients for whom emergency or urgent surgery would represent a significant additional risk, it may be a valuable temporary measure permitting stabilization of the patient's condition.

References

1. **Kilpatrick ZM, Chapman CB:** On pericardiocentesis. Am J Cardiol 16:722–728, 1965
2. **Spodick DH:** Acute cardiac tamponade. Pathologic physiology and management. Prog Cardiovasc Dis 10:64–96, 1967
3. **Bishop LH Jr, Estes EH Jr, McIntosh HD:** Electrocardiogram as a safeguard in pericardiocentesis. JAMA 162:264–265, 1956
4. **Owens WC, Schaefer RA, Rahimtoola SH:** Pericardiocentesis: insertion of a pericardial catheter. Catheterization and Cardiovasc Diagnosis 1:317–321, 1975
5. **Glancy DL, Richter MA:** Catheter drainage of the pericardial space. Catheterization and Cardiovasc Diagnosis 1:311–315, 1975
6. **Luft FC, Kleit SA, Smith RN, et al:** Management of uremic pericarditis with tamponade. Arch Intern Med 134:488–490, 1974
7. **Busselmier TJ:** Persistent uremic pericardial effusion: pericardial drainage and localized steroid instillation as definitive therapy. Abstracts of 6th Annual Meeting, American Society of Nephrology, Washington, DC, 1973, p 18
8. **Lokich JJ:** The management of malignant pericardial effusions. JAMA 224:1401–1404, 1973
9. **Biran S, Brufman G, Klein E, et al:** The management of pericardial effusion in cancer patients. Chest 71:182–186, 1977

Discrete Subaortic Stenosis in Adults

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Discrete subaortic stenosis tends to be a progressive, severe defect that occurs most often in children. Of 138 patients who underwent operation for this defect at the Texas Heart Institute and affiliated hospitals from 1956 to 1976, only 36 patients (26 percent) were adults. The clinical, hemodynamic and surgical findings and follow-up data of these 36 patients, aged 18 to 65 years, are reviewed. The high incidence rate of associated cardiac defects and bacterial endocarditis is emphasized. Follow-up information, available for 22 of the original 36 patients, revealed three perioperative and two late deaths. One patient died 6 months after operation of unknown cause, and another died 4 years later of myocardial infarction. Fifteen of the 17 known survivors are asymptomatic or in improved condition.

The symptoms and electrocardiographic findings of discrete subaortic stenosis are similar to those of aortic valve stenosis. The presence of an aortic ejection click or calcification of the valve on chest roentgenography or fluoroscopy indicates a diagnosis of valve stenosis. The usual criteria for diagnosis, localization of the gradient below the aortic valve at cardiac catheterization or angiographic demonstration of discrete subaortic stenosis, are not always evident. Echocardiography may aid in determining the diagnosis by demonstrating early systolic closure of the aortic valve leaflets. An acceptable low surgical mortality rate can be achieved; however, some patients require aortic valve replacement or multiple operations for adequate repair of their defect. Patients with a thin membrane generally have a more favorable result than those with a fibromuscular collar or secondary muscular hypertrophy. Aortic regurgitation is not always predictable and may recur or progress postoperatively.

Since its first description by Chevers[1] in 1842, congenital discrete subaortic stenosis has been recognized as a cause of obstruction of the left ventricular outflow tract. This anomaly accounts for 10 to 20 percent of all cases of congenital aortic stenosis.[2–6] Most patients reported on[3–14] are younger than 18 years of age. Brock[13] once suggested that subvalve aortic stenosis is a severe lesion that usually causes death before adulthood in untreated patients. Other reports,[3,14–16] including data from serial hemodynamic studies, also support this observation of rapid progression of obstruction in patients with subaortic stenosis. In this study we review the clinical, hemodynamic and surgical results of discrete subaortic stenosis in 36 adults.

Materials and Methods

From 1956 to 1976, a total of 138 patients with discrete subaortic stenosis were operated on at the Texas Heart Institute and affiliated hospitals. Thirty-six of these patients (26 percent) were adults, ranging in age from 18 to 65 years (Fig. 1). Patients younger than age 18 years were excluded from the study. All 36 patients underwent surgical correction of their cardiac defects. Before operation right and left heart catheterization was performed in 30 patients, and right heart

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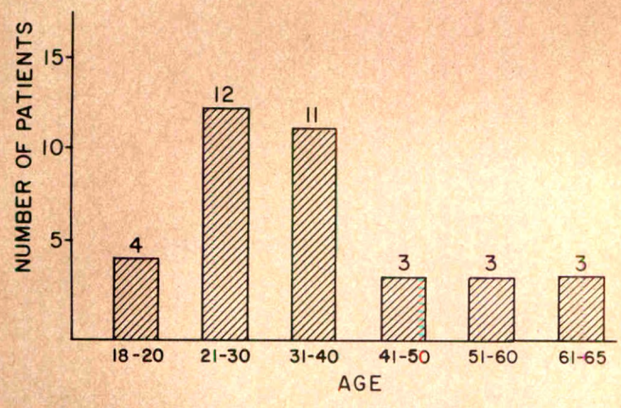

FIGURE 1. Distribution of age (in years) in 36 adult patients with discrete subaortic stenosis.

catheterization alone in 2. A repeat cardiac catheterization was performed postoperatively in seven patients.

Cardiac catheterization: This procedure was usually performed with mild sedation and no general anesthesia. The left ventricle was entered in a retrograde manner from the brachial artery. The gradient across the site of obstruction was obtained with a pullback pressure recording from the apex of the left ventricle to the ascending aorta. All pressure measurements were recorded before left ventricular angiography. An aortic root angiogram was also obtained to assess the severity of aortic regurgitation.

Surgical procedures: Operation involved resection of the subaortic membrane or collar alone, or resection plus aortic valve replacement and repair of the associated defects, depending on the findings in each patient. All patients underwent operation by staff surgeons using techniques described previously.[7,17,18] Temporary cardiopulmonary bypass with disposable plastic-bubble oxygenators primed with 5 percent dextrose was used, and the patient's body temperature was maintained at normothermic levels. Operations were performed through a median sternotomy. A transverse or oblique incision was made approximately 1 cm above the coronary ostia to ensure adequate visualization of the valve and subvalve areas. The fibrous membrane was excised with a knife or scissors, avoiding the anterior leaflet of the mitral valve. Coronary perfusion was not used in patients who had resection alone because of the short length of time required for this procedure. Cardiac hypothermia was usually used in the patients who required concomitant replacement of the aortic valve or repair of associated defects. Recently, cold cardioplegic techniques with potassium chloride diluted in Ringer's lactate solution at 4° C have been used to accomplish hypothermia.

Results

Clinical Description

Types, age and sex: Two major types of discrete subaortic stenosis, similar to those classified by Kelly et al.,[11] were noted at the time of operation (Fig. 2). Type I, in which a thin discrete membrane is generally located a few millimeters below the valve, was found in 23 of our patients. Type II, in which a fibromuscular

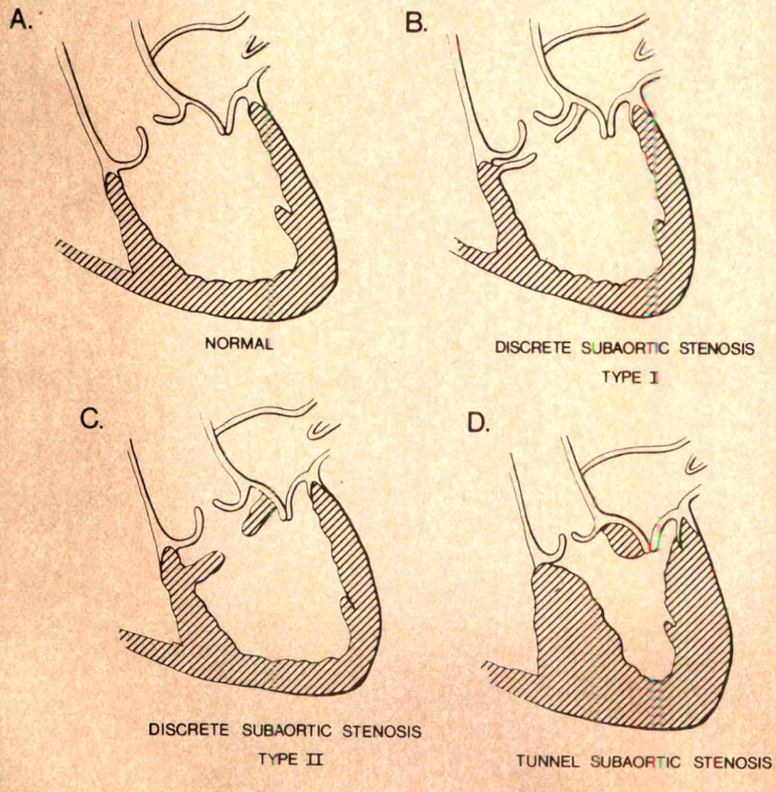

FIGURE 2. Diagrammatic illustration of a normal heart **(A)** and the salient features of hearts with discrete subaortic stenosis. There is a thin membrane in type I **(B)** and a fibromuscular collar in type II **(C)**. Both types may or may not be associated with muscular hypertrophy. Tunnel subaortic stenosis **(D)** is a diffuse type of left ventricular outflow tract obstruction and is frequently associated with a small aortic anulus.

collar usually less than 1 cm thick tends to be situated slightly lower than the membrane in type I, was noted in 13 patients. Patients with both types may have associated muscular hypertrophy without significant outflow obstruction. Fourteen men and 9 women had type I stenosis (male/female ratio 1.6:1), and 7 men and 6 women had type II (male/female ratio 1.2:1). The oldest patient with type I stenosis was aged 65 years and the oldest with type II, 62 years. Thirty patients (83 percent) were less than 50 years old.

History: The most common symptoms, in order of decreasing frequency, were exertional dyspnea, chest pain, palpitations, easy fatigability and syncope (Table I). Chest pain, usually atypical in presentation, occurred in 26 patients (72 percent) and was related to exertion in only 8. The presenting symptoms of discrete subaortic stenosis were similar to those of aortic valve stenosis. There was no definite correlation between the systolic pressure gradient and symptoms.

Twenty-nine patients (80 percent) had a history of a heart murmur; nine (25 percent) had a history of bacterial endocarditis, and evidence of the infection was found on the aortic valve at operation. In two other patients bacterial endocarditis developed after resection of the subaortic membrane.

Physical findings: No significant physical differences were found between patients with type I and II stenosis. Nine patients had a prominent left ventricular impulse. A diastolic murmur of aortic insufficiency was audible in 21 patients (58 percent) (Table II). Thirteen of these 21 patients had severe aortic insufficiency and required aortic valve replacement in addition to resection of the subaortic obstruction. In six patients new murmurs of aortic insufficiency developed 6 to 8 years after resection. In patients whose condition was uncomplicated by aortic regurgitation, the clinical findings were similar to those of aortic valve stenosis. Systolic murmur, narrow pulse pressure and delayed and prolonged carotid upstroke were common findings. No patient had an ejection click on auscultation.

TABLE I

Clinical Presentation of 36 Adult Patients With Discrete Subaortic Stenosis

Finding	no. of Patients		Total	
	Type I	Type II	no.	%
Exertional dyspnea	18	11	29	80
Chest pain	16	10	26	72
Palpitations	8	4	12	33
Fatigue	6	3	9	25
Syncope	7	2	9	25
Dizziness	3	2	5	14
Orthopnea	3	0	3	8.3
Pulmonary edema	0	2	2	5.5
Embolism	1	1	2	5.5
History of murmur	18	11	29	80
Bacterial endocarditis	6 (plus 2 postop)	3	9	25
Rheumatic fever	3	0	3	8.3

TABLE II

Objective Findings in 36 Adult Patients With Discrete Subaortic Stenosis

Finding	no. of Patients
Systolic murmur	36
Diastolic murmur	21
Cardiomegaly	21
Left ventricular hypertrophy	30
Pressure gradient from left ventricle to aorta	29 (of 30)

Noninvasive Laboratory Data

Roentgenographic findings: The chest roentgenogram on admission showed evidence of moderate to severe cardiomegaly in 11 patients. Ten patients had only slight cardiac enlargement, predominantly with a left ventricular configuration. Heart size was normal in 15 patients. Chest roentgenography revealed no calcification of the aortic valve in any patient. Slight dilatation of the ascending aorta was noted in three patients, one with severe and two with only minimal aortic insufficiency. The size of the heart generally did not correlate with the symptoms or the severity of hemodynamic obstruction.

Echocardiography: Echocardiograms were recorded in 10 patients after 1972. Only seven of these recordings were considered technically adequate for analysis (1974 and later). Three patients with isolated subaortic membrane (type I) had early systolic closure of the aortic leaflet (Fig. 3A); in one of these patients the aortic valve movement reverted to normal after resection of the membrane (Fig. 3B). This finding was not evident in the four other patients with associated anomalies. Aortic leaflets causing multiple echoes in diastole and poor separation of echoes in systole were demonstrated in two patients with a calcified stenotic aortic valve. Eccentric and triangular closure of an aortic leaflet was found in one patient with severe aortic insufficiency. Asymmetric septal hypertrophy and systolic anterior movement of the mitral valve were found in one patient with subaortic membrane and hypertrophic subaortic stenosis. Unfortunately, the aortic leaflets were not visualized clearly in this patient.

Cardiac Catheterization

Of the 30 patients who underwent left heart catheterization, 4 had studies, performed at other institutions, in which the site of outflow obstruction could not be crossed. Twenty-six patients had a peak systolic gradient across the left ventricular outflow tract ranging from 0 to 168 mm Hg. The gradient could be localized below the valve by pullback pressure recording in only seven patients (Fig. 4).

Eight patients had a gradient of more than 100 mm Hg and 12 a gradient of 50 to 100 mm Hg. A gradient of less than 35 mm Hg was found in only two patients; both had severe aortic insufficiency and a dilated aortic anulus (Table II). One patient had no gradient but did have surgical findings of a subaortic membrane at the

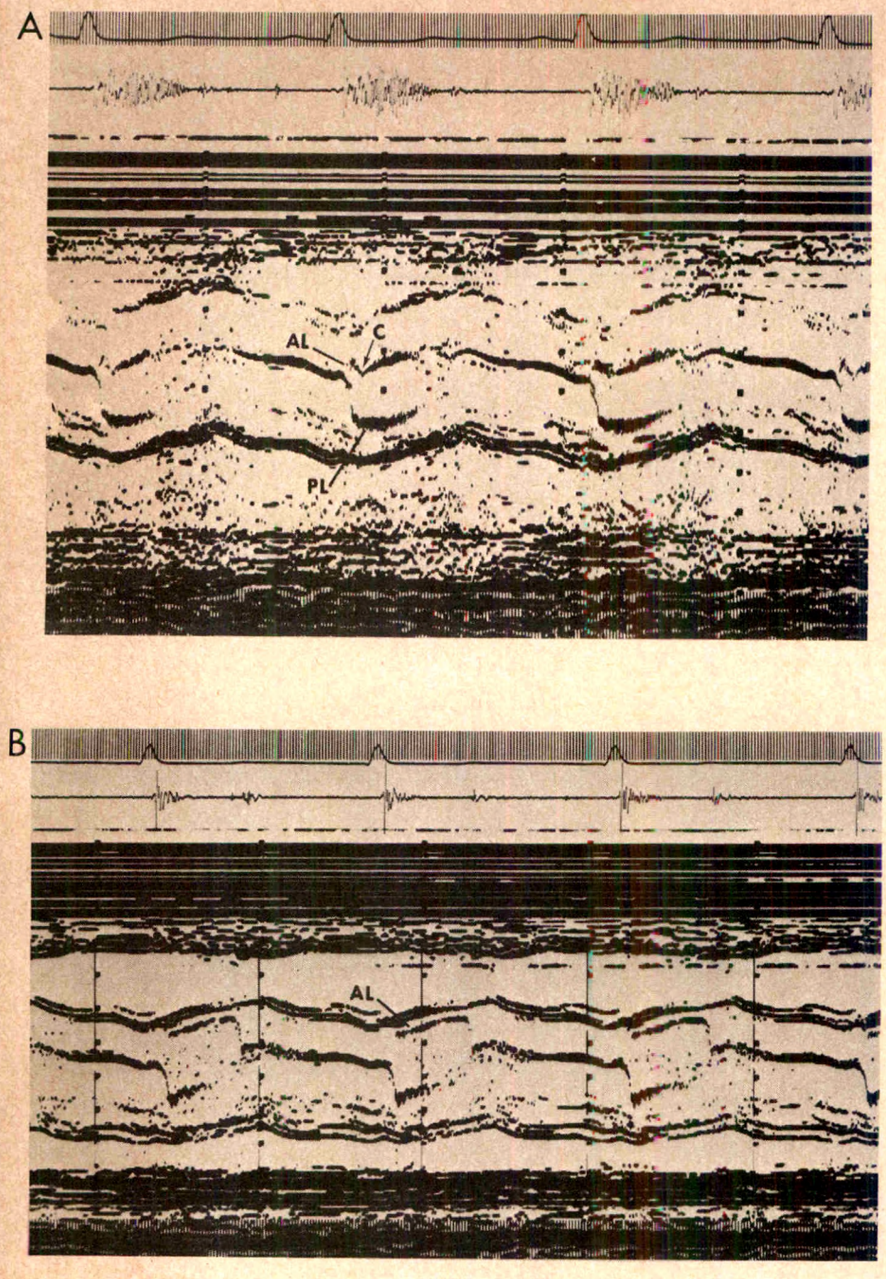

FIGURE 3. Echocardiographic findings in a patient with type I discrete subaortic stenosis. **A,** preoperative, showing typical early systolic closure (C) of aortic leaflets. **B,** postoperative, after resection of discrete subaortic membrane. The aortic valve leaflets now revert to normal movement. AL = anterior leaflet; PL = posterior leaflet.

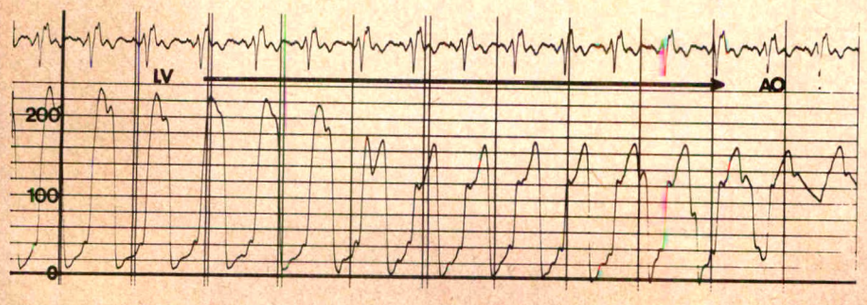

FIGURE 4. Illustration of pullback pressure recording from the left ventricle (LV) to the aorta (AO), showing a pressure gradient from the body to the subaortic region of the left ventricle.

TABLE III

Operative Mortality Data

Case no.	Age (yr)	Procedure	Abnormality	Remarks
1	19	Resection, AVR	Fibromuscular collar, AS, infantile aortic anulus, interstitial fibrosis of heart muscle	Died 6 days after operation
2	21	Resection	Fibromuscular collar, diffuse hyperplasia of thryoid (Graves')	Reexploration to remove hematoma 6 days after resection; died 12 days after resection
3	40	Resection, AVR	Fibromuscular collar, AS, AI, MR	Sudden death 3 weeks postoperatively, probably pulmonary embolism

AI = aortic insufficiency; AS = aortic stenosis; AVR = aortic valve replacement; MR = mitral regurgitation.

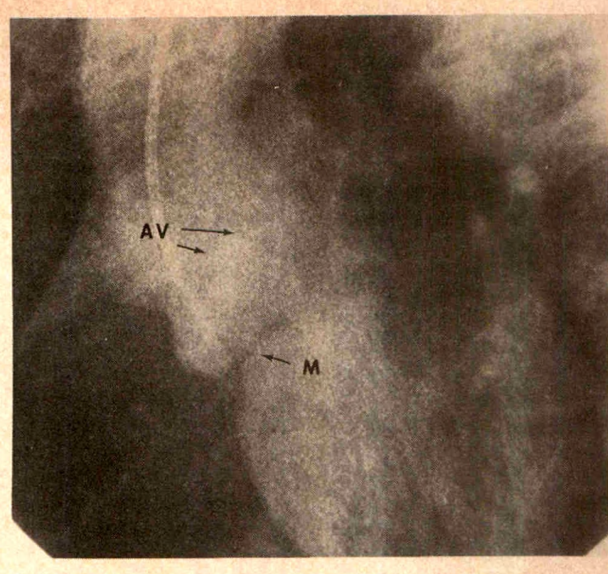

FIGURE 5. Left ventriculogram in left anterior oblique view showing a thin nonopacified membrane (M) below the aortic valve (AV).

TABLE IV

Associated Cardiac Defects in 17 Patients With Discrete Subaortic Stenosis

Defect	no. of Patients
Aortic valve stenosis	5
Bicuspid aortic valve	2
Muscular hypertrophic subaortic stenosis	3
Supravalve obstruction	2
Aneurysm of sinus of Valsalva	1
Infantile aortic anulus	1
Patent ductus arteriosus and ascending aortic aneurysm	1
Patent ductus arteriosus	1
Subpulmonary infundibular stenosis	1

time of aortic valve replacement for severe aortic insufficiency.

Left ventriculography typically revealed a thin nonopacified line below the aortic valve (Fig. 5). The difference between a thin membrane and a fibromuscular collar was only a matter of degree. On angiographic examination aortic regurgitation was found in 24 patients, whereas diastolic murmurs were audible in 21. At times, aortic root angiography aided in visualizing the membrane in the presence of aortic insufficiency.

Operation

All 36 patients underwent surgical correction. Resection of the subaortic membrane or collar alone was performed in 12 patients. Eight patients required aortic valve replacement at the time of resection. Seven patients had resection plus correction of associated cardiac defects. Resection, aortic valve replacement and correction of associated defects were performed concomitantly in four patients. In four patients the initial resection was followed years later by a second operation (aortic valve replacement) for aortic insufficiency. One patient had recurrent obstruction of the left ventricular outflow tract, consisting of a membrane and muscular hypertrophic subaortic stenosis. He was initially treated with dilatation of the outflow tract, then by resection of the membrane 12 years later and eventually by placement of a conduit from the left ventricle to the abdominal aorta 18 years after the first operation. After the last operation the subaortic gradient decreased from 120 to 35 mm Hg, and the patient's condition improved notably.

There were three postoperative deaths (8 percent): two hospital deaths and a third death occurring less than 30 days after operation (Table III).

Associated Cardiac Defects

In addition to discrete subaortic stenosis, congenital cardiac defects were found in 17 patients (47 percent) (Table IV). All but one of the anomalies involved the left side of the heart. Acquired lesions occurred in 75 percent of our patients, most of whom had aortic insufficiency. Three patients had valvular heart disease caused by rheumatic fever. All older patients and most younger adults who undergo left heart catheterization at this institution now also undergo selective coronary arteriography. However, many of the patients described in this report were studied elsewhere or several years earlier, when selective coronary injection was not performed as routinely as it is at present. Eight of our patients underwent selective coronary arteriography; two had coronary stenosis. Twenty-two patients underwent aortic root arteriography, which revealed no significant coronary stenosis grossly.

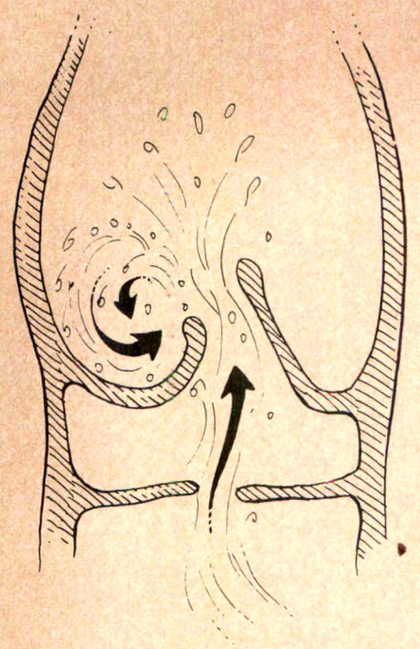

FIGURE 6. Diagrammatic illustration of turbulent jet flow of blood through the subaortic membrane and aortic valve, causing lesions to the aortic cusps.

Discussion

Despite several previous studies[3,14–16] suggesting that discrete subaortic stenosis is hemodynamically progressive, a substantial proportion of our 138 patients (26 percent) reached adulthood before the onset of symptoms. A similar age distribution was reported in two relatively small series,[4,12] in which 20 to 22 percent of the patients were adults. Our oldest patient was 65 years of age.

More adults than children were symptomatic. Eighty percent of our adult patients had exertional dyspnea, compared with a 17 percent incidence rate reported in children.[14] In contrast, only two of our adults had severe congestive heart failure, and both had associated valve lesions secondary to rheumatic fever and congenital aortic valve stenosis, respectively. Newfeld et al.[14] found congestive heart failure in 7 of 51 children with discrete subaortic stenosis.

Aortic regurgitation: Acquired aortic insufficiency in patients with discrete subaortic stenosis has been described previously.[19] It is believed to be secondary to the turbulent flow of blood that causes damage to the aortic cusps[10] (Fig. 6). The jet lesions are usually mild unless there is complicating infective endocarditis. Occasionally, severe aortic insufficiency may be found without the secondary infection that occurred in three of our patients. Thirty to 55 percent of pediatric patients with discrete subaortic stenosis had aortic regurgitation.[5,9–11,14] In our series of adult patients, 66 percent (24 patients) had aortic regurgitation. In more than half of the patients, the regurgitation was severe enough to require aortic valve replacement. Of the 12 patients who underwent resection of the subaortic membrane or collar alone, 6 had a murmur of aortic insufficiency 6 to 8 years after resection. This implies either recurrence of stenosis or damage to the aortic cusps preoperatively with the development of incompetence years after the resection. In general, aortic insufficiency is more prevalent and severe in adults than in children.

Bacterial endocarditis: The high incidence rate of bacterial endocarditis in patients with discrete subaortic stenosis has been emphasized. Fontana and Edwards[20] found evidence of endocarditis or its sequelae at postmortem examination in 13 of 29 patients (45 percent). The incidence of bacterial endocarditis increases with age. None of the 25 children reported on by Kelly et al.[11] had endocarditis. In our adult group 25 percent (nine patients) had vegetative growth on the aortic leaflets at the time of surgery. Resection of the subaortic membrane or collar did not prevent the occurrence of endocarditis after operation in two of our patients. Predisposition to infection can be explained in terms of either the preexisting jet lesion or the recurrence of stenosis. The former is probably the more likely explanation because thickening of the aortic valve was present in most patients. Prophylactic antibiotic therapy should be given to prevent endocarditis at times of potential bacteremia and therefore is indicated in all patients throughout life. It is conceivable that early resection of the membrane may prevent further trauma to the aortic cusps and lessen the chance of infection.

Type of obstruction: Differentiation and surgical results: The two types of discrete subaortic stenosis differ only in degree, with the fibromuscular collar (type II) usually being thicker and situated lower than the thin membrane (type I). Variable degrees of muscular hypertrophy of the left ventricle can occur secondary to the stenosis in either type. Progressive resolution of the hypertrophic muscle has been reported[8] after resection. Discrete subaortic stenosis should be distinguished from idiopathic muscular hypertrophic subaortic stenosis. Secondary obstruction caused by muscular hypertrophic stenosis was found in three of our patients with a discrete subaortic membrane. The surgical results in these patients were usually less satisfactory. In one patient, a conduit connecting the left ventricle to the abdominal aorta was eventually required to alleviate the obstruction. Similar disappointing results have been reported by others.[11–14] Patients with type I stenosis generally have better surgical results than those with type II. It is not known whether discrete subaortic stenosis, muscular hypertrophic subaortic stenosis and so-called "tunnel subaortic stenosis"[21] share the same pathogenesis.

Associated defects: Associated cardiac defects have been found in 10 to 57 percent of patients with discrete subaortic stenosis.[4,5,8–11,14] Aortic valve stenosis,[4,14] either bicuspid or tricuspid, patent ductus arteriosus,[5,8,10,11,14] coarctation of the aorta,[5,8,10,11,14] persistent left superior vena cava,[5,8,11] ventricular septal defect,[5,8–11,14] incomplete atrioventricular canal,[8] double outlet right ventricle,[8] pulmonary valve stenosis,[8,10,11]

subpulmonary infundibular stenosis,[9] parachute mitral valve[22] and supravalve aortic stenosis[9] have been reported to coexist with discrete subaortic stenosis. With the exception of pulmonary stenosis and persistent left superior vena cava, all of these anomalies primarily involve the left side of the heart (for example, the so-called multiple congenital lesions of the left heart). These anomalies frequently mask the diagnosis of discrete subaortic stenosis.[14] Occasionally, noncardiac defects such as tuberous sclerosis have also been described.[23] Congenital anomalies were found in 47 percent of our adult patients. No patient had a ventricular septal defect, coarctation of the aorta or persistent left superior vena cava. Perhaps the most impressive associated defects in adults are the acquired lesions that occurred in 75 percent of our patients. Jet lesions, bacterial endocarditis, rheumatic fever and atherosclerotic heart disease are the common causes.

Differential diagnosis: The similarity of the clinical manifestations of aortic valve stenosis and discrete subaortic stenosis presents a challenge to clinicians. The symptoms of the two defects are similar. An audible aortic ejection click is rare in reported series of subaortic stenosis (despite occasional demonstration on phonocardiography). We found no aortic ejection click in our patients. The click also tends to become increasingly rare with advancing age in patients with aortic valve stenosis; thus its presence is mainly of interest in the pediatric group, in whom it is a valuable clue to the diagnosis of aortic valve stenosis. Although an audible early diastolic murmur of aortic regurgitation is more common in patients with discrete subaortic stenosis, it is frequent enough in adults with aortic valve stenosis to be of no help in differentiating the two defects.

Calcification of the aortic valve on roentgenography or fluoroscopy clearly indicates a primary valve abnormality[4,24] but does not always exclude a second level of obstruction. The electrocardiogram provides no help in differentiating the defects.

Angiographic demonstration of the membrane and pressure gradients on withdrawal of the catheter from the left ventricle to the aorta has been the basis for diagnosis of subaortic stenosis in the past. If present, the gradients are helpful, but often the membrane is so close to the valve that a subaortic chamber is not demonstrated[25]; only seven of our patients had an unequivocal *sub*valve gradient. Selective left ventriculography and thoracic aortography usually demonstrate the subaortic stenosis, but sometimes even with more than one view, the findings are not clear-cut.

Echocardiography has recently emerged as a useful aid in differentiating the various forms of left ventricular outflow obstruction. Early systolic closure of the aortic valve in patients with discrete subaortic stenosis has been reported[26] and is quite specific for this disorder. Figure 3 illustrates the typical early systolic closure of the aortic valve preoperatively with postoperative reversion to normal.[27] Although early systolic closure of the aortic valve can also be seen in patients with idiopathic hypertrophic subaortic stenosis, the valve usually closes much later than in patients with discrete subaortic stenosis. In addition, echocardiographic evidence of asymmetric septal hypertrophy and systolic anterior movement of the mitral valve is not found in most patients with discrete subaortic stenosis.

The high incidence rate of associated cardiac defects, whether congenital or acquired, often adds to the difficulty of diagnosing discrete suboartic stenosis. Newfeld et al.[14] reported that in 65 percent of their pediatric patients, the diagnosis of subaortic stenosis was initially masked by associated cardiac defects. In adults the left ventricular outflow tract obstruction was more obvious, and the major task was to localize the lesion.

Criteria for operation: When adults with significant aortic stenosis or insufficiency, or both, have reached the stage of significant symptoms (preferably early class III, New York Heart Association functional classification[28]), it has become accepted procedure to perform aortic valve replacement. The development of congestive heart failure, syncope or chest pain is a more serious finding in patients with pure valve stenosis. Large gradients across the valve, even without symptoms, have often prompted operation, particularly in children, in whom calcification has not occurred and commissurotomy may be successful without valve replacement.

Several reports[3,14–16] of serial hemodynamic studies in patients with discrete subaortic stenosis provide convincing evidence that this lesion is progressive in nature, particularly during the growth period. Most authors[8,14] agree that a gradient of 40 to 50 mm Hg or more is a reasonable indication for surgery, especially if there is a thin membrane below the valve. It is still debatable whether early surgery prevents progressive aortic valve disease, including regurgitation in the patient with discrete subaortic stenosis. We hope that reducing the turbulent jet flow through the subaortic stenotic area will result in less progression and less chance of subsequent infective endocarditis. In uncomplicated cases surgery can be accomplished with a low level of risk. In a previous study[7] we had no operative deaths in 25 patients (primarily children) who underwent resection of the subaortic membrane. In the present series there were only three perioperative deaths in 41 operations (7.3 percent); all three patients who died had severe medical problems in addition to the subaortic stenosis.

Follow-up: Of the original 36 adult patients operated on during the past 20 years, follow-up information is available on 22 (61 percent). In addition to the three patients who died in the perioperative period, two patients died later: one suddenly at home 6 months postoperatively (presumably of cardiac causes, but no postmortem examination was performed) and another of massive myocardial infarction 4 years postoperatively. Most (13) of the remaining survivors are asymptomatic; the condition of two survivors is improved, and two have symptoms similar to their preoperative symptoms.

Clinical implications: Results in this group of patients, as in others from previous reports, indicate that discrete subaortic stenosis is not always easily relieved surgically. Patients with a localized membrane and no

other heart defects who are operated on early in life appear to have a better chance for excellent long-term results. We speculate that the aortic valve tends to be damaged from a turbulent jet flow through the subaortic membrane or collar, presumably with progressive deterioration through the years necessitating aortic valve replacement more often in the older patient. There is also a tendency in some for the stenosis to recur or progress postoperatively; this is more likely in patients with a fibromuscular collar or in those in whom a dynamic type of secondary muscular hypertrophy develops. Nevertheless, the condition of even this group may be improved with more aggressive surgery, as in the patient who underwent a third operation to have a valved conduit attached from the left ventricular apex to the abdominal aorta.

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References

1. **Chevers N:** Observations on the diseases of the orifice and valves of the aorta. Guys Hosp Rep 7:387–442, 1842
2. **Keith JD, Rowe RD, Vlad P:** Heart Disease in Infancy and Childhood (second edition). New York, MacMillan, 1967, p 250
3. **Lambert EC, Colombi M, Wagner HR, et al:** The clinical outlook of congenital aortic stenosis (valvar and discrete subvalvar) prior to surgery. In, The Natural History and Progress in Treatment of Congenital Heart Defects, chap 29 (Kidd BSL, Keith JD, ed). Springfield, IL, Charles C Thomas, 1971, p 205
4. **Braunwald E, Goldblatt A, Aygen MM, et al:** Congenital aortic stenosis. I. Clinical and hemodynamic findings in 100 patients. II. Surgical treatment and the results of operation. Circulation 27: 426–462, 1963
5. **McGoon DC, Geha AS, Scofield EL, et al:** Surgical treatment of congenital aortic stenosis. Dis Chest 55:388–394, 1969
6. **Lillehei CW, Bonnabeau RC Jr, Sellers RD:** Subaortic stenosis, diagnostic criteria, surgical approach, and late follow-up in 25 patients. J Thorac Cardiovasc Surg 55:94–104, 1968
7. **Cooley DA, Beall AC Jr, Hallman GL, et al:** Obstructive lesions of the left ventricular outflow tract: surgical treatment. Circulation 31:612–621, 1965
8. **Reis RL, Peterson LM, Mason DT, et al:** Congenital fixed subvalvular aortic stenosis: an anatomical classification and correlations with operative results. Circulation 43, 44:Suppl I:I-11–I-18, 1971
9. **Shariatzadeh AN, King H, Girod D, et al:** Discrete subaortic stenosis: a report of 20 cases. J Thorac Cardiovasc Surg 63:258–262, 1972
10. **Champsaur G, Trusler GA, Mustard WT:** Congenital discrete subvalvar aortic stenosis: surgical experience and long-term follow-up in 20 pediatric patients. Br Heart J 35:443–446, 1973
11. **Kelly DT, Wulfsberg E, Rowe RD:** Discrete subaortic stenosis. Circulation 46:309–322, 1972
12. **Deutsch V, Shem-tov A, Yahini JH, et al:** Subaortic stenosis (discrete form): classification and angiocardiographic features. Radiology 101:275–286, 1971
13. **Brock R:** Aortic subvalvar stenosis: surgical treatment. Guys Hosp Rep 108:144–158, 1959
14. **Newfeld EA, Muster AJ, Paul MH, et al:** Discrete subvalvular aortic stenosis in childhood: study of 51 patients. Am J Cardiol 38:53–61, 1976
15. **El-Said G, Galioto FM, Mullins CE, et al:** Natural hemodynamic history of congenital aortic stenosis in childhood. Am J Cardiol 30:6–12, 1972
16. **Mody MR, Mody GT:** Serial hemodynamic observations in congenital valvular and subvalvular aortic stenosis. Am Heart J 89: 137–143, 1975
17. **Hallman GL, Cooley DA:** Surgical Treatment of Congenital Heart Disease (second edition). Philadelphia, Lea & Febiger, 1975, p 70–71
18. **Cooley DA, Norman JC:** Techniques in Cardiac Surgery. Houston, Medical Press, 1975, p 136
19. **Morrow AG, Fort L III, Roberts WC, et al:** Discrete subaortic stenosis complicated by aortic valvular regurgitation: clinical, hemodynamic and pathological studies and the results of operative treatment. Circulation 31:163–171, 1965
20. **Fontana RS, Edwards JE:** Congenital Cardiac Disease: A Review of 357 Cases Studied Pathologically. Philadelphia, WB Saunders, 1962, p 214
21. **Maron BJ, Redwood DR, Roberts WC, et al:** Tunnel subaortic stenosis: left ventricular outflow tract obstruction produced by fibromuscular tubular narrowing. Circulation 54:404–416, 1976
22. **Shone JD, Sellers RD, Anderson RC, et al:** The developmental complex of "parachute mitral valve," supravalvular ring of left atrium, subaortic stenosis, and coarctation of aorta. Am J Cardiol 11:714–725, 1963
23. **Adyanthaya AV, Price EC, Miller GV, et al:** Membranous subvalvular aortic stenosis in tubular sclerosis. Chest 61:407–408, 1972
24. **Glancy DL, Epstein SE:** Differential diagnosis of type and severity of obstruction to left ventricular outflow. Prog Cardiovasc Dis 14:153–191, 1971
25. **Brock R, Fleming PR:** Aortic subvalvar stenosis. Guys Hosp Rep 105:391–408, 1956
26. **Davis RH, Konecke LL, Dillon JC, et al:** Echocardiographic findings in discrete subaortic stenosis (abstr). Am J Cardiol 31:127, 1973
27. **Younis AG, Awdeh M, Benrey J, et al:** Discrete membranous subaortic stenosis: postoperative reversion of aortic valve echocardiogram to normal. Cardiovasc Dis, Bull Texas Heart Institute 3:424–429, 1976
28. Criteria Committee of the New York Heart Association: Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels, seventh edition. Boston, Little, Brown, 1973, p 286

Diagnosis of Dissecting Aortic Aneurysm With Suprasternal Echocardiography

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A 33 year old woman with Marfan's syndrome and aortic root dissection was studied with precordial and suprasternal echocardiography. The precordial approach revealed some typical features of aortic root dissection. With suprasternal echocardiography it was possible to visualize the characteristic diagnostic feature of this disease: within the aortic lumen an m-shaped pattern—the aortic intimal flap—moving downward to the posterior aortic wall during systole. The diagnosis was confirmed with aortic cineangiography and intraoperative findings. Thus, suprasternal echocardiography can be a useful method of detecting aortic root dissection, especially in patients with aortic arch dissection alone.

Precordial echocardiography has been reported[1–10] to be a useful approach in detecting aortic root dissection. However, the echocardiographic patterns described have not always been in accordance with the clinical diagnosis.[6,11] Echographic diagnosis of aortic dissection can be improved with use of the suprasternal approach, as demonstrated in the following patient with dissecting aortic aneurysm who was studied before and after operation.

Case Report

A 33 year old woman with the classic features of Marfan's syndrome was referred to the hospital for cardiac catheterization. Two months before admission she had an attack of severe retrosternal pain of sudden onset.

Physical examination revealed a blood pressure of 130/90 mm Hg in the right arm and 90/70 mm Hg in the left arm. A grade 3/4 systolic ejection murmur was heard over the aortic area and was palpable in the jugular notch. The second heart sound was followed by a grade 2/4 diastolic murmur. The chest roentgenogram revealed an enlarged ascending aorta with a normal left ventricle and normal pulmonary arteries. At cardiac catheterization, moderate aortic regurgitation was found. The left ventricular end-diastolic and pulmonary arterial pressures were normal.

Cineangiograms of the aortic root were obtained by injection of 75 ml of 76 percent Urografin® in the ascending aorta with a flow of 25 ml/sec (see Fig. 4). The cineangiograms showed a marked dilatation of the ascending aorta. Immediately after injection the true aortic lumen was contrasted densely whereas the false channel in delay was visualized by faint contrast. A fluttering intimal structure separated both lumens. In systole this dissected inner wall moved downward to the posterior aortic wall and produced a narrowing of the true aortic lumen. The dissection was found to extend to the abdominal aorta.

Echocardiographic studies: These studies were performed using a Smith-Kline Ekoline 20 ultrasonoscope interfaced with a Cambridge recorder and a nonfocused 0.5 inch (1.27 cm) transducer with a frequency rate of 2.25 megahertz. Suprasternal notch echocardiograms were performed with the method of Goldberg.[12] The contrast echocardiograms were obtained during cardiac catheterization. Injection of 1 ml of indocyanine green dye followed by a rapid injection of isotonic saline solution was used to produce the contrast effects. This

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solution was injected either into the pulmonary artery or by way of an atrial transseptal catheter into the left ventricle. No echocardiogram was obtained with the catheter in aortic root position.

Precordial echocardiogram: This showed a normal-sized left ventricle with an exaggerated motion pattern of the posterior left ventricular wall and the interventricular septum. A fine fluttering of the anterior mitral leaflet suggested aortic insufficiency. There was no evidence of pericardial effusion. Scanning the aortic root showed a marked widening from 45 to 63 mm (end-systolic outer diameter). The anterior aortic wall thickness was 8.9 mm. The anterior aortic wall moved anteriorly during systole and consisted of several solid lines moving in parallel throughout the cardiac cycle; the posterior aortic wall showed an abnormal bulging posteriorly. The aortic cusp motion caused a most striking pattern showing a wide cusp separation of 48 mm (normal range 15 to 26 mm[13]), caused mainly by the posterior motion of the noncoronary leaflet. This finding was confirmed by injection of contrast medium in the left ventricle, resulting in a shower of microbubbles entering the aortic root during valve opening (Fig. 1).

Suprasternal echocardiogram: With the suprasternal approach, the aortic root diameter was found to be widened to 32 mm (normal range 21.7 ± 3.8 mm[12]). Tilting of the transducer anteriorly and to the left revealed an m-shaped pattern

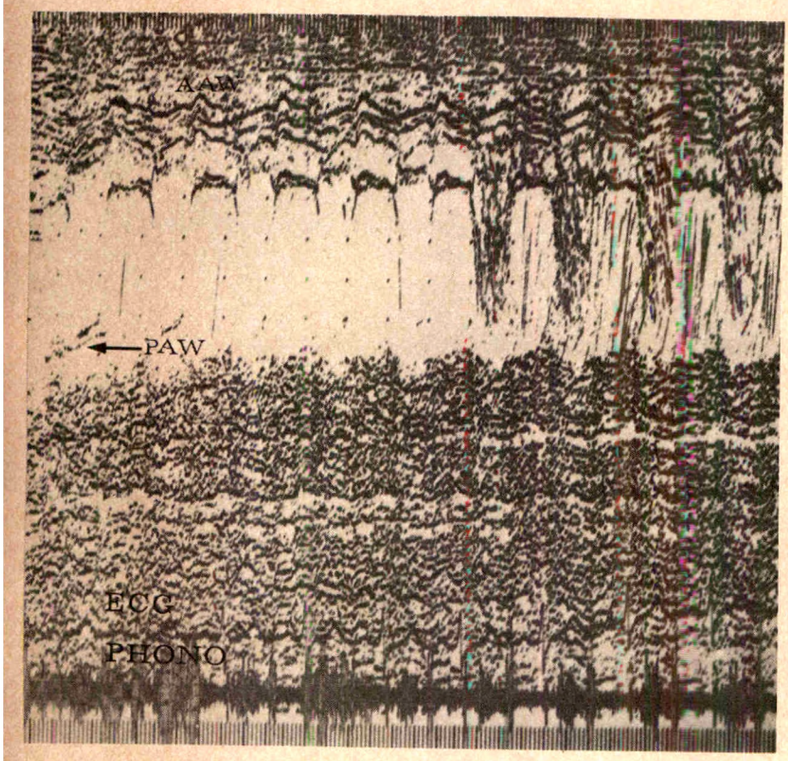

FIGURE 1. Precordial echocardiogram of the aortic root before and during injection of contrast medium. AAW = anterior aortic wall; ECG = electrocardiogram; PAW = posterior aortic wall; PHONO = phonocardiogram.

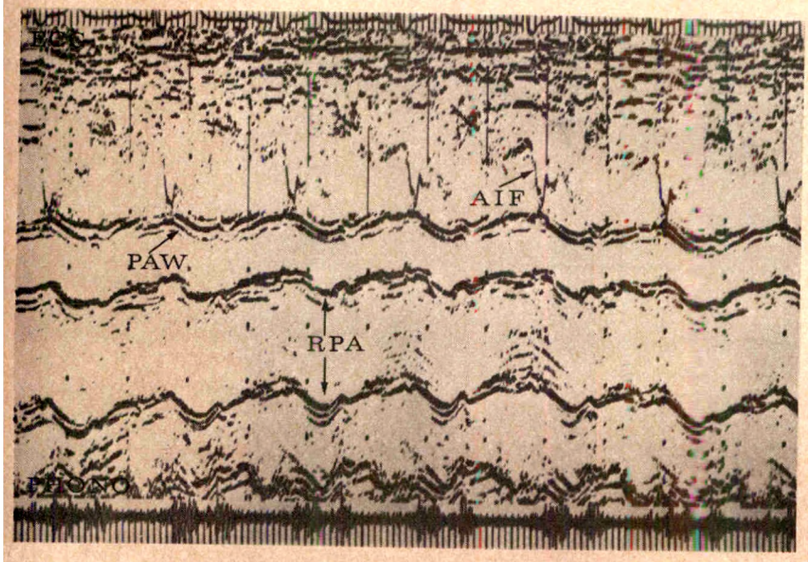

FIGURE 2. Suprasternal echocardiogram of the aortic root. The transducer was tilted from the caudad position anteriorly and to the left. In this position the anterior aortic wall was not visualized. Notice the stretched scale, which was chosen for better demonstration of the aortic intimal flap (AIF). ECG = electrocardiogram; PAW = posterior aortic wall; RPA = right pulmonary artery.

moving downward to a solid line. This pattern was thought to be the fluttering of an aortic intimal flap (Fig. 2). The anterior aortic wall could not be visualized in this position. Contrast echocardiograms obtained during aortic and pulmonary angiography (Fig. 3) again demonstrated the m-shaped pattern, the shower of microbubbles allowing localization of the aortic lumen.

Aortic cineangiography: Identification of the m-shaped pattern as the aortic intimal flap was supported by aortic cineangiographic findings (Fig. 4), showing that the intimal flap moved downward to the posterior aortic wall during systole, thus leading to a narrowing of the true aortic lumen.

Surgical findings and treatment: At cardiac surgery, an aortic dissection covering the distance between the aortic valves and the abdominal aorta was found. Approximately two thirds of the aortic circumference was involved in the dissection. The aortic intima remained attached to the media in only a small area of the posteromedial aortic wall. At operation, parts of the aneurysmal aortic wall were removed and the dissected layers were reunited at the site of the intimal tear.

Postoperative echocardiographic studies, performed 3 weeks later, showed the following features: The size of the aortic root in the precordial echocardiographic scan was slightly reduced from 63 to 55 mm; however, a much more pronounced alteration had occurred in the pattern of aortic cusp motion and on the posterior aortic wall (Fig. 5). Cusp widening was normalized (24 mm), suggesting that the bulging of the posterior leaflet had been greatly reduced by the an-

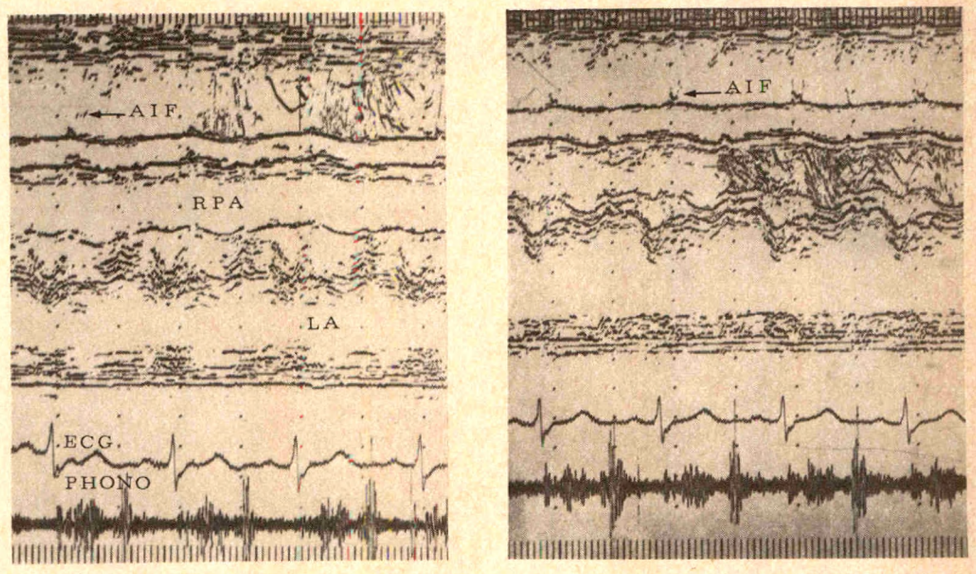

FIGURE 3. Suprasternal contrast echocardiograms during cardiac catheterization with injection of contrast medium into the left ventricle (**left panel**) and pulmonary artery (**right panel**). AIF = aortic intimal flap; ECG = electrocardiogram; LA = left atrium; PHONO = phonocardiogram; RPA = right pulmonary artery.

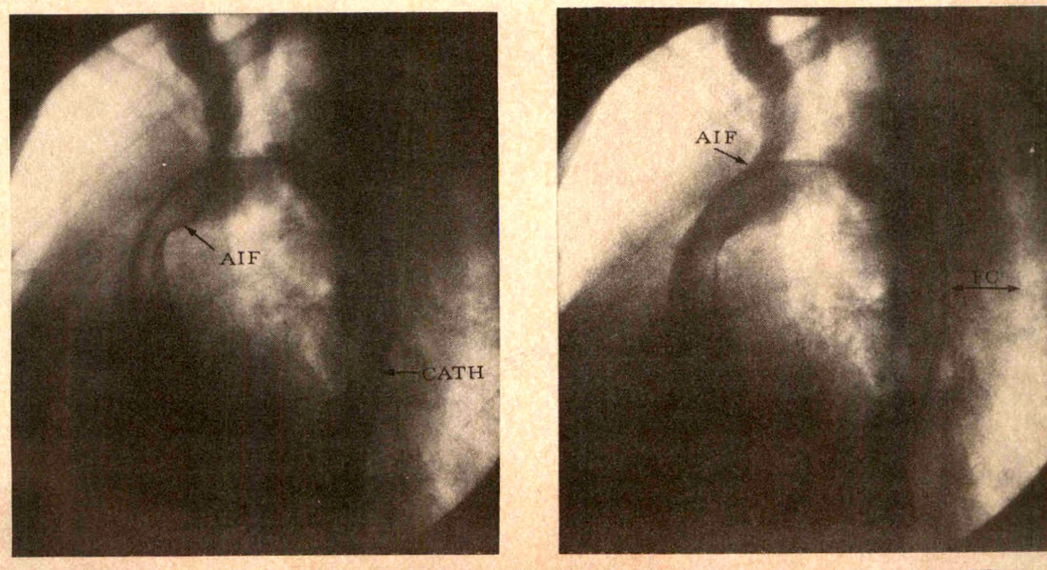

FIGURE 4. Cineangiograms of the aortic root during systole (**left panel**) and diastole (**right panel**). The aortic intimal flap (AIF) moved downward to the posterior aortic wall and produced a narrowing of the true aortic lumen. Faint contrast material visualized the false channel (FC). CATH = catheter.

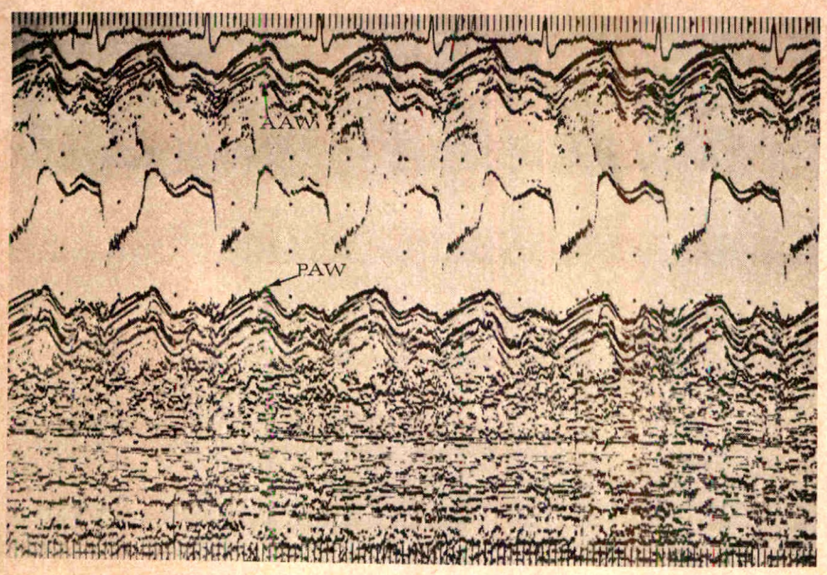

FIGURE 5. Precordial echocardiogram after aneurysmectomy. No bulging of the posterior aortic cusp could be demonstrated, and the posterior aortic wall (PAW) consisted of several solid lines moving anteriorly during systole. AAW = anterior aortic wall.

eurysmectomy whereas systolic fluttering of the leaflets still was present. The preoperatively visualized bulging of the posterior wall could not be demonstrated. During systole the posterior wall showed an anterior movement. Both the posterior and the anterior wall were represented by several solid lines moving in parallel throughout the cardiac cycle. No fluttering structure could be detected with suprasternal echocardiography although the aortic root was scanned in different positions at different times.

Discussion

In 1971 Goldberg[12] developed the theory that the suprasternal echocardiogram might be a useful method of detecting aortic root dissection. Until recently several investigators proposed precordial echocardiography for ultrasonic diagnosis of aortic dissection; however, this method has pitfalls.[6,11] Some echocardiographic criteria for aortic root dissection, such as widening of the aortic root and multiple parallel echoes of the aortic walls, were also seen in patients with aortic root dilatation alone.[5,9] Especially in cases with aortic arch dissection without involvement of the ascending aorta, the precordial approach is of no or only minor value.[9] In our case initially the precordial approach led us to suggest that aortic dissection had taken place. A marked widening of the aortic root as well as parallel echoes within the anterior aortic wall were observed. Nevertheless, our patient appeared to present an interesting variant in that the noncoronary cusp showed a marked bulging toward the posterior wall. This abnormality suggested involvement of the aortic valve ring by dissection and has not been described in previous echocardiographic studies on aortic root dissection.

Using the suprasternal approach we were able to see the motion of the aortic intimal flap. Thus one of the most characteristic features[10] of an aortic dissection could be visualized. The echocardiographic findings were confirmed with aortic cineangiography and the intraoperative findings. Whether the loosened aortic intima can regularly be observed with suprasternal echocardiography in aortic dissection involving the aortic arch awaits confirmation. At least, the finding of such a structure within the lumen of the aorta does stress the diagnosis of a dissected aortic aneurysm.

Suprasternal echocardiography appears to be of diagnostic value for two reasons: (1) It allows detection of aortic arch dissection alone; (2) in cases of extended dissections beginning in the ascending aorta, involvement of the aortic arch can be demonstrated.

References

1. **Millward DK, Robinson NJ, Craige E:** Dissecting aortic aneurysm diagnosed by echocardiography in a patient with rupture of the aneurysm into the right atrium. Am J Cardiol 30:427–431, 1972
2. **Nanda NC, Gramiak R, Shah PM:** Diagnosis of aortic root dissection by echocardiography. Circulation 58:506–513, 1973
3. **Kronzon I, Mehta SS:** Illustrative echocardiogram: aortic root dissection. Chest 65:88–89, 1974
4. **Yuste P, Aza V, Minguez I, et al:** Dissecting aortic aneurysm diagnosed by echocardiography. Br Heart J 36:111–113, 1974
5. **Moothart RW, Spangler RD, Blount SG:** Echocardiography in aortic root dissection and dilatation. Am J Cardiol 36:11–16, 1975
6. **Brown OR, Popp RL, Kloster FE:** Echocardiographic criteria for aortic root dissection. Am J Cardiol 36:17–20, 1975
7. **Drobinski G, Nivet G, Grosgogeat Y, et al:** Echocardiographic d'un cas de dissection aortique. Nouv Presse Med: 5:570–572, 1976
8. **Tricot R, Valère PE, Houeix JM, et al:** Etude echocardiographique de deux cas de dissection aortique. Arch Mal Coeur 69:891–898, 1976
9. **Di Luzio V, Purcaro A, Boccanelli A, et al:** La diagnosi ecocardiografica di dissezione dell'aorta toracica. G Ital Cardiol 6:677–685, 1976
10. **Curati WL, Peticlerc R, Dyroa I, et al:** Echographic demonstration of mobility of the dissecting flap of an aortic aneurysm. Radiology 123:173–174, 1977
11. **Krueger SK, Starke H, Forker AD, et al:** Echocardiographic mimics of aortic root dissection. Chest 67:441–444, 1975
12. **Goldberg BB:** Suprasternal ultrasonography. JAMA 215:245–250, 1971
13. **Feigenbaum H:** Echocardiography. Philadelphia, Lea & Febiger, 1976, p 464

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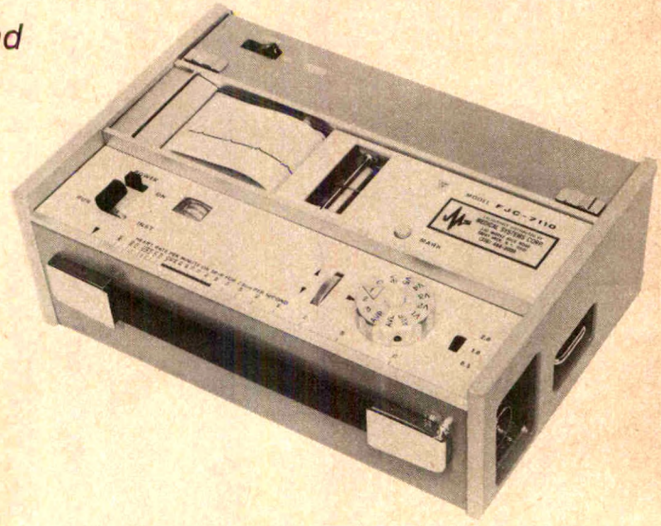

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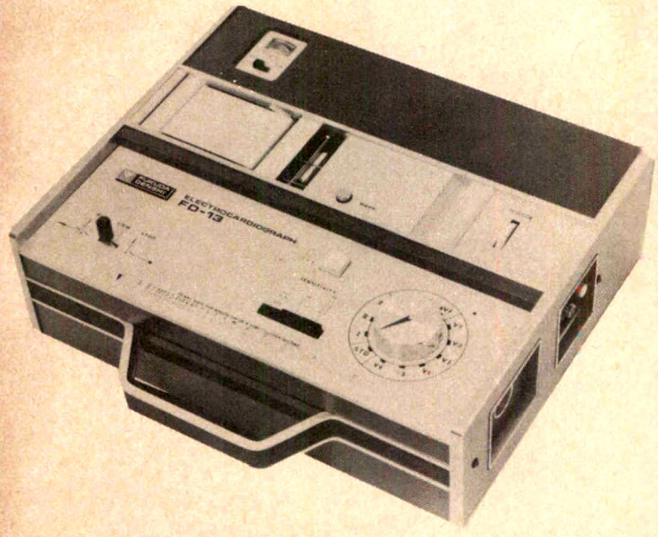

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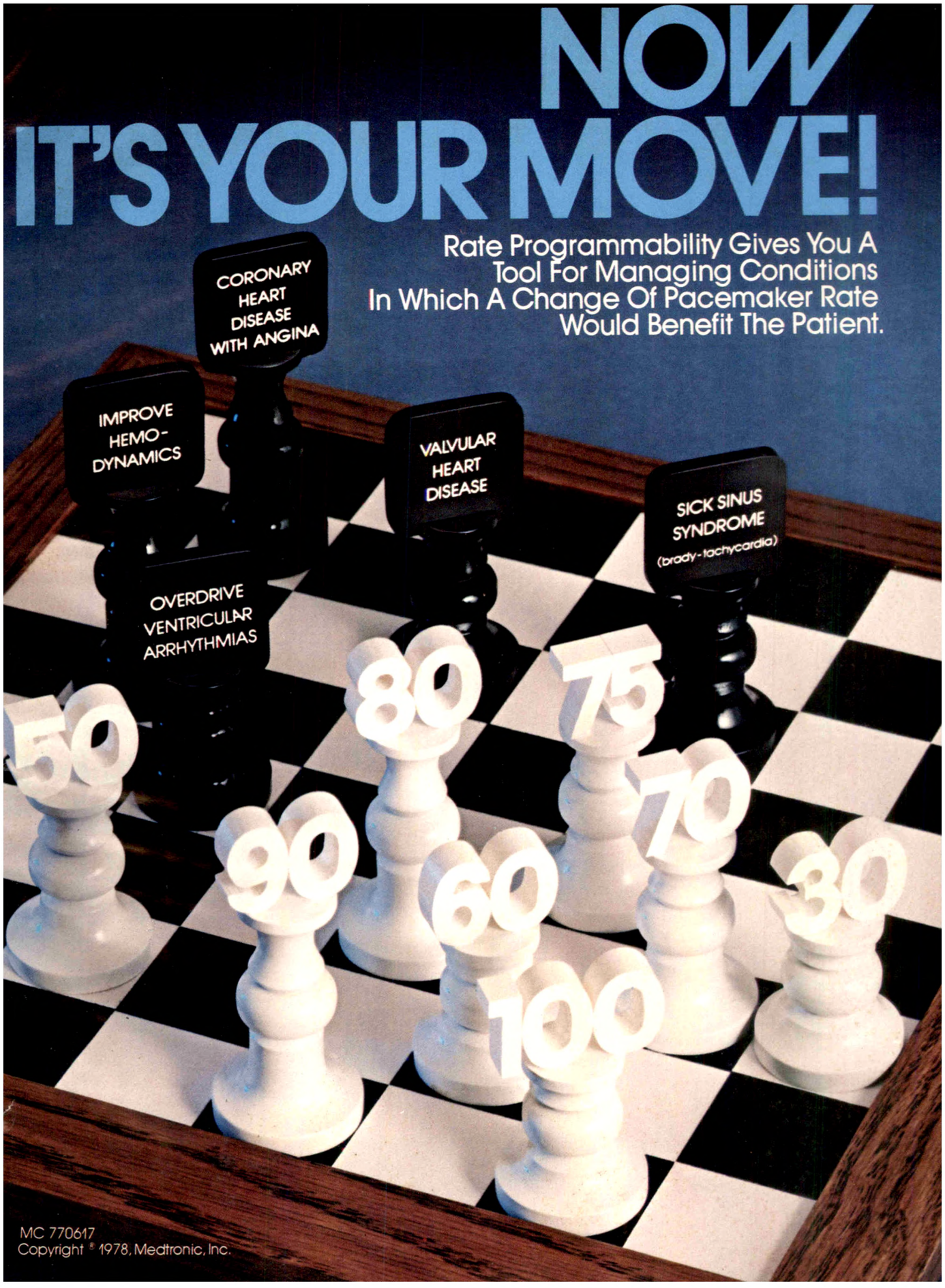
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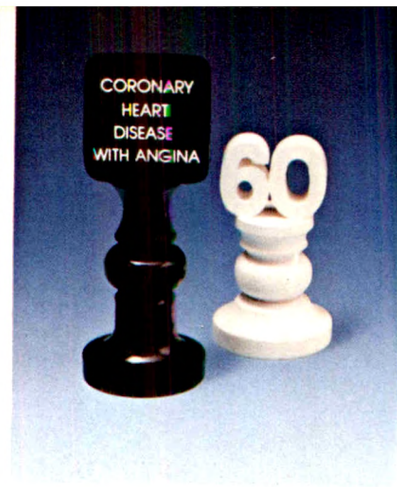
1. Sick Sinus Syndrome (brady-tachycardia).
2. Coronary heart disease with angina pectoris.
3. Valvular heart disease.
4. To overdrive ventricular arrhythmias.
5. To improve hemodynamics.

In each of these, having the ability to change the pacing rate can preserve, maintain or improve the quality of life for pacemaker patients. Furthermore, because of the potential longevity of lithium pacemakers, the physician can take advantage of the greater flexibility provided by rate programmability to respond to the patient's changing medical condition during the pulse generator service life.



USING RATE PROGRAMMABLE PACEMAKERS IN CORONARY HEART DISEASE WITH ANGINA PECTORIS

Not infrequently, the patient in whom pacing is indicated presents with coronary artery disease and angina pectoris.

Angina may be occurring as a consequence of heart rate exceeding the ability of the coronary artery network to provide adequate circulation to myocardial tissue. Since heart tissues receive nutrients during diastole, it is felt that a slower heart rate and a corresponding longer diastolic period may provide enhanced opportunity for energy and oxygen transfer to myocardial tissue.

In any event, a rate programmable pacemaker permits evaluation for clinical symptoms at various rates and can permit selection of a pacing rate which is not likely to provoke angina, while providing the patient with adequate exertional status.

THE APPLICATION OF RATE PROGRAMMING IN BRADY-TACHYCARDIA (SICK SINUS SYNDROME).

After the physician has determined that artificial heart pacemaking is the treatment of choice for the patient with brady-tachycardia, he may contemplate application of a rate-programmable pacemaker to treat this disease.

Because brady-tachycardia may be a progressive disease, it is often appropriate to implant a rate-programmable pacemaker.

For example, in the early stages of the disorder, the patient may require pacing for just a few seconds a month when the intrinsic rate drops below a rate which the physician has determined provides adequate cardiac output. In such a situation, the pacemaker is set at a low rate (i.e., 50 or 60 ppm) to provide an underlying safe rhythm, but which allows the patient the benefit of his normal atrial ventricular contraction sequence.

Sick sinus syndrome at times is a progressive disorder which may result in a slowing of the patient's normal sinus rhythm. This slowing may be gradual or sudden. Frequently, it is accompanied by a tendency towards a more unreliable rhythm. The patient, thus, increases his or her reliance on the pacemaker for adequate heart rate.

Rate programming at increasingly higher rates may help maintain cardiac output at adequate levels when the pacemaker is needed to provide the dominant rhythm. An increase in pacemaker rate may also be needed to prevent the emergence of a less suitable tachyarrhythmia.

THE APPLICATION OF RATE PROGRAMMABLE PULSE GENERATORS IN VALVULAR HEART DISEASE

The clinical course for pacemaker patients with valvular heart disease is complex and unpredictable.

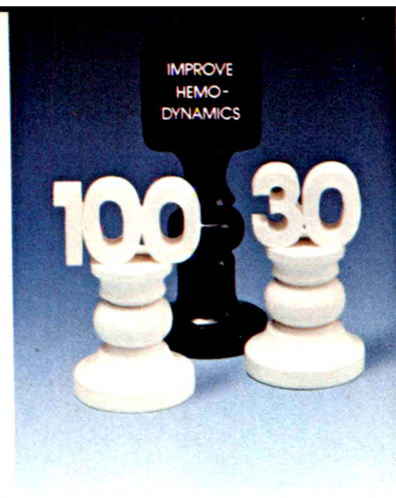
Many of these patients require a pacemaker prior to operation for their valve lesion.

The patient with aortic stenosis may need to have his rate adjusted to a slow level to allow for complete emptying of the ventricle. Too fast a rate increases ventricular pressure and restricts the flow of blood from the coronary arteries to the endocardium, resulting in subendocardial ischemia. There is some evidence that pacing at typical fixed pacemaker rates may actually cause patients with aortic stenosis to lose cardiac output and have decreased perfusion pressure.

On the other hand, the patient with aortic insufficiency has regurgitation backwards into the ventricle. A slow rate allows more blood to flow backwards, increasing volume and ventricular pressure. This also restricts blood flow from the coronary arteries to the endocardium, again resulting in subendocardial ischemia. A faster paced rate may help control the condition. Of course, the best rate for perfusing the endocardium for either condition varies considerably between patients.

Rate requirements will probably change a great deal when a prosthetic valve replacement is made.

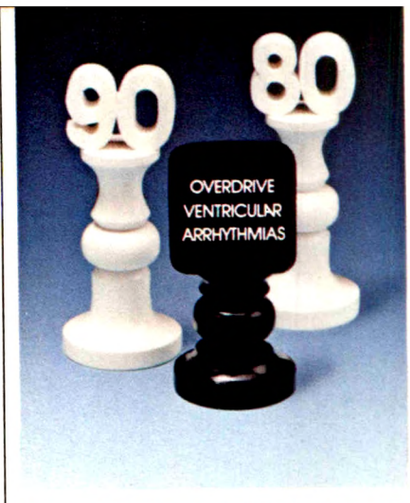
Typically, any patient with valvular heart disease who requires a pacemaker could benefit from the flexibility a rate-programmable pacemaker offers in this complex, unpredictable disorder.



CHANGING RATE TO ENHANCE THE METABOLIC STATE THROUGH IMPROVED HEMODYNAMICS

Conditions of disease, or certain medical treatments, can affect a patient's metabolic requirements. Pacemaker patients are, because of their age and underlying heart disease, prone to various medical problems, including myocardial infarction, angina and congestive heart failure.

By having the ability to alter the diseased or ill patient's heart rate, the physician can optimize the rate for maximum cardiac output and organ perfusion without affecting (or with minor effects) on myocardial oxygen uptake. Also, in some MI patients a rate can be found which produces increased cardiac output with decreased left ventricular filling pressure. Rate changes may also affect and improve a patient's mental state and enhance the ability to perform even mild exercise. When a pacemaker is implanted, the patient is ill (i.e. bed-ridden). An adequate rate under those conditions may not be adequate when the patient is up and about.



USE OF RATE PROGRAMMABLE PACEMAKERS TO CONTROL VENTRICULAR ARRHYTHMIAS

Ectopic ventricular activity can be suppressed by permanent pacing. However, the slowest paced rate at which ventricular arrhythmias will be controlled is unpredictable, and changeable. It is not unusual for the rate at which PVC's occur to change as the patient's underlying heart disease progresses.

Pacing in the presence of PVC's often involves considerable adjusting of rate as the physician determines the paced rate which will be just slightly higher than the rate at which the ectopic foci discharge. This rate may involve a compromise, for an optimal rate for achieving maximal cardiac output may not coincide with the best rate for suppressing ectopic activity. Indeed some pacemaker rates tend to excite reentry pathways causing the extra-systole.

For these reasons, having the opportunity to change rate can assist the physician in arrhythmia control.

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CONTRAINDICATIONS There are no known contra-indications to the use of pacing as a therapeutic modality for the control of heart rate. The patient's age and medical condition, however, may dictate the particular pacing systems and implantation procedure used by the physician.

WARNINGS Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of unipolar pulse generators or bipolar pulse generators implanted in the unipolar mode because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator.

PRECAUTIONS The physician should be aware that all pulse generators will ultimately cease to function, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, and elevated thresholds, and that proper operation may be affected by electrical interference from equipment using electrical energy, or medical complications.

SIDE EFFECTS Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.

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WARNING
Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats (see *Warnings*). Aldactone should be used only in those conditions described under *Indications*. Unnecessary use of this drug should be avoided.

Indications: Diagnosis and treatment of primary hyperaldosteronism. Essential hypertension, edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate. Cirrhosis of the liver accompanied by edema and/or ascites. Hypokalemia.

Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, or hyperkalemia.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactone. Do not administer concurrently with other potassium-sparing diuretics.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75, and 250 times the usual daily human dose (2 mg./ kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hyponatremia may be caused or aggravated, especially when Aldactone is administered in combination with other diuretics. Transient elevation of BUN and/or mild acidosis may occur. Aldactone potentiates the effect of other diuretics or antihypertensive agents, particularly ganglionic blocking agents: therefore the dosage of such drugs should be reduced by at least 50 percent when adding Aldactone. Gynecomastia may develop and in rare instances some breast enlargement may persist. Vascular responsiveness to norepinephrine may be reduced.

Spironolactone may cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazard to the fetus. Breast feeding should be discontinued when Aldactone is being used.

Adverse Reactions: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established. Adverse reactions are usually reversible upon discontinuation of the drug.

Dosage and Administration

For primary hyperaldosteronism: 400 mg. daily for three to four weeks (long test), or for four days (short test). For preparation for surgery or for long-term maintenance therapy, 100 to 400 mg. daily.

For edema in adults: Initial daily dosage is 100 mg. in divided doses but may range from 25 to 200 mg. daily. If after five days an adequate diuretic response has not occurred, a second diuretic which acts more proximally in the renal tubule may be added. The dosage of Aldactone should remain unchanged when other diuretic therapy is added.

For edema in children: Initial daily dosage should provide approximately 1.5 mg. per pound of body weight (3.3 mg./kg.) in divided doses.

For essential hypertension: Initial adult daily dosage of 50 to 100 mg. in divided doses, alone or with diuretics which act more proximally in the renal tubule, or with other antihypertensive agents. Continue treatment for at least two weeks since maximal response may not occur before this time. Adjust subsequent dosage according to patient response.

For hypokalemia: 25 to 100 mg. daily in divided doses.

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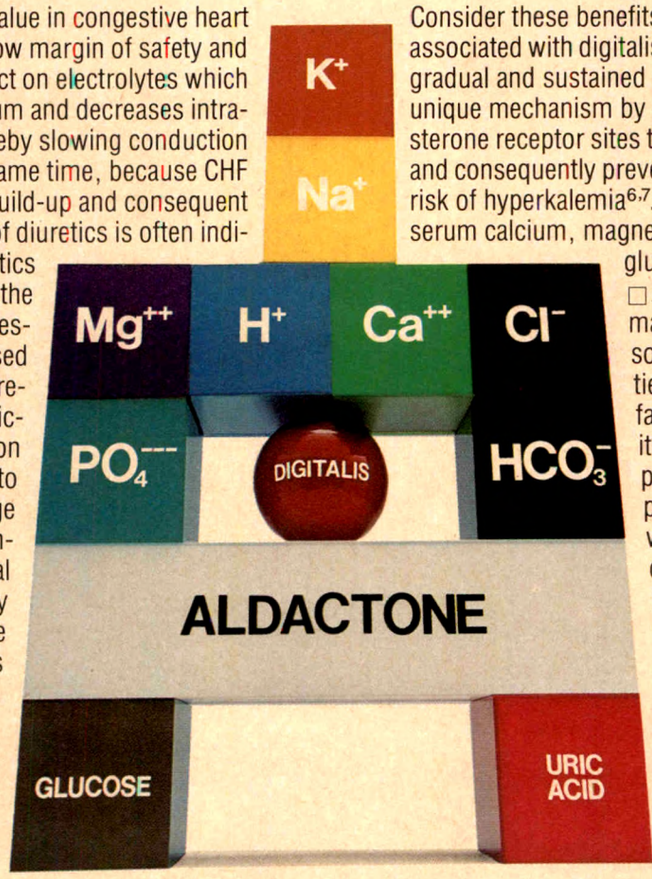
The Delicate Balance.

Unfortunately, electrolyte imbalance is often a problem during digitalis therapy. And most diuretics worsen the problem.

Despite its therapeutic value in congestive heart failure, digitalis has a narrow margin of safety and toxic levels produce an effect on electrolytes which increases intracellular sodium and decreases intracellular potassium, thereby slowing conduction in cardiac tissues. At the same time, because CHF encourages sodium build-up and consequent edema, concomitant use of diuretics is often indicated. □ Use of most diuretics can increase problems for the patient on digitalis, and excessive loss of potassium caused by potent diuretics is a frequent cause of digitalis toxicity.[1,2] Potassium depletion sensitizes the myocardium to digitalis and can set the stage for serious cardiac arrhythmias even with normal dosage.[3] □ Clearly, any diuretic choice should be carefully analyzed for its effect on electrolyte balance. Thiazides, for example, can induce hypokalemia, hypercalcemia, hypomagnesemia, and hypophosphatemia.[4] They can also decrease uric acid excretion and impair glucose tolerance. In treatment with furosemide, too, fluid and electrolyte imbalance is the most common form of clinical toxicity.[5]



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Consider these benefits in avoiding the problems associated with digitalis therapy: Aldactone provides gradual and sustained diuresis...works through a unique mechanism by which it competes for aldosterone receptor sites to normalize body potassium, and consequently prevents hypokalemia with limited risk of hyperkalemia[6,7]...does not adversely affect serum calcium, magnesium and uric acid levels or glucose tolerance.[7]

□ Aldactone is indicated for management of edema and sodium retention in those patients with congestive heart failure who are taking digitalis, or in the treatment or prevention of hypokalemia in patients taking digitalis, when other measures are considered inadequate or inappropriate. □ When diuretic therapy is indicated, prescribe Aldactone to help preserve the delicate balance of electrolytes during digitalis therapy.

1. Kirkendall, W.M.: What's With Hypertension These Days? Consultant *11*:13-15 (Jan.) 1971.
2. Maronde, R.F.; Milgrom, M. and Dickey, J.M.: Potassium Loss with Thiazide Therapy, Am. Heart J. *78*:16-21 (July) 1969.
3. Cardiac Glycosides, Section 4, in Kastrup, E. K. (Editor): Facts and Comparisons, St. Louis, Facts and Comparisons, Inc., Jan. 1975, pp. 140-141C.
4. Weibert, R. T.: Heading Off Adverse Reactions. Thiazide Diuretics, Curr. Prescr. *3*:62-69 (Oct.) 1977.
5. Mudge, G. H., Diuretics and Other Agents Employed in the Mobilization of Edema Fluid, Chapter 39, in Goodman, L. S., and Gilman, A. (Editors): The Pharmacological Basis of Therapeutics, ed. 5., New York, Macmillan Publishing Co., Inc., 1975, pg. 836.
6. Laragh, J. H.: Diuretics in the Management of Congestive Heart Failure, Hosp. Pract. *5*:43-50 (Nov.) 1970.
7. Tobian, L. J., Jr.: The Clinical Approach to Essential Hypertension, Hosp. Pract. *10*:33-44 (July) 1975.

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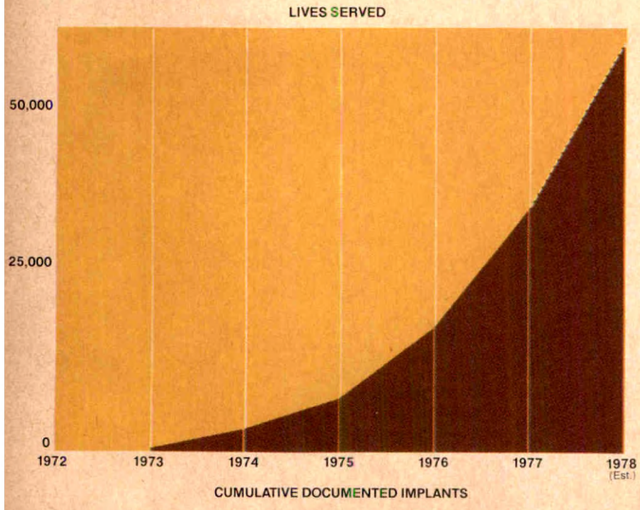

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Sanford Levine, Senior Vice President and Director of Kaufman and Broad, Inc., a multi-national homebuilding corporation based in Los Angeles, is actively involved in his company after a CPI Microlith ,-P was implanted to replace his previous pacemaker. "I find that I am not even aware of my CPI pacemaker. Levine says. "The company s record for reliability with pacemakers has given me peace of mind.

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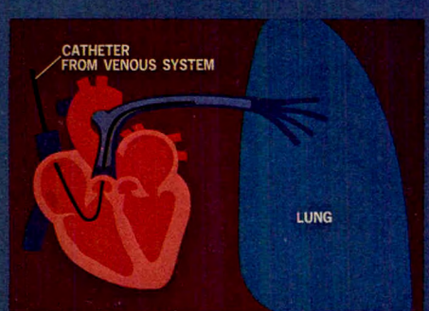
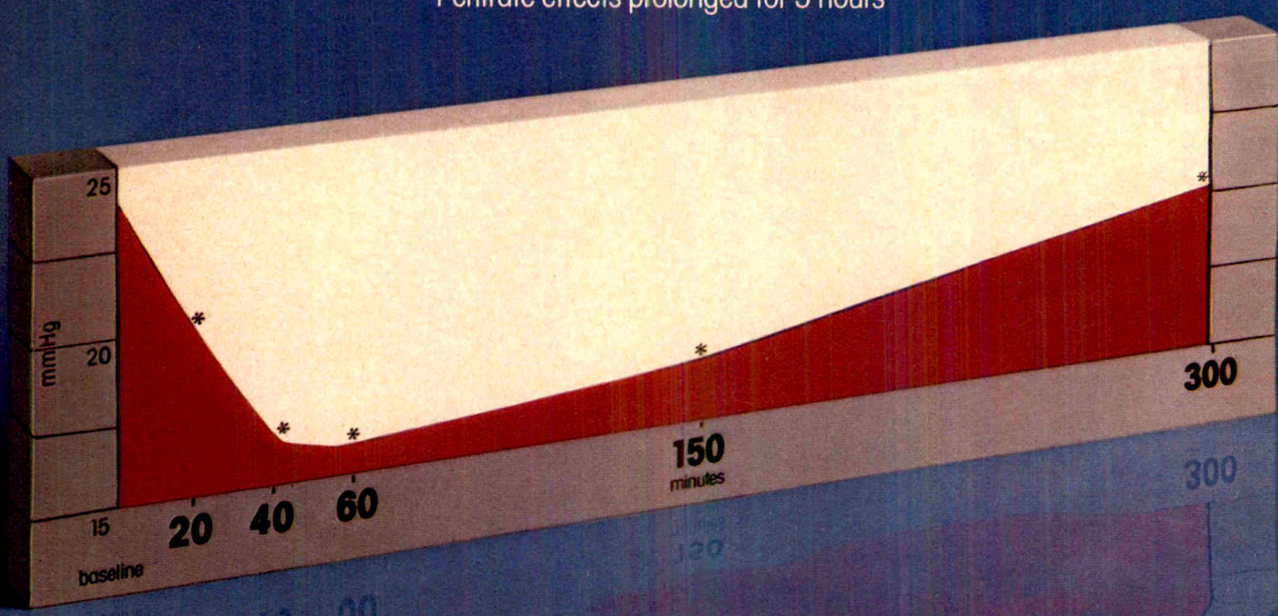


In a randomized double-blind study of catheterized patients with congestive heart failure, Peritrate 40 mg demonstrated marked changes in a variety of hemodynamic parameters with no change in heart rate.[1]

A marked reduction in PRELOAD: Peritrate reduced pulmonary arterial wedge pressure for over 300 minutes. The maximum reduction was 37%. Pulmonary arterial mean pressure was also reduced for over 300 minutes. These manifestations of reduced PRELOAD resulted from an increase in venous capacitance leading to a reduction in left ventricular end-diastolic volume and pressure. The observed reduction in pulmonary wedge pressure indicates marked preload reduction.

Peritrate effects prolonged for 5 hours



A reduction in AFTERLOAD: A significant reduction of arterial blood pressure, correlating with reduced AFTERLOAD, was maintained for over 300 minutes.[1]

Reduction in blood pressure for 5 hours

parameter	before Peritrate n=12	60 minutes after Peritrate n=12	150 minutes after Peritrate n=12	300 minutes after Peritrate n=8
blood pressure (mmHg) systolic	122.6	116.7*	116.9	116.8*
diastolic	68.7	63.4*	61.3*	61.0*

*Statistically significant at the 5% level.

Peritrate actions observed

- Activity was prolonged for at least 5 hours.
- PRELOAD and AFTERLOAD showed a marked reduction lasting at least 5 hours.

1. Klein RC, Amsterdam EA, Pratt C, et al: Sustained reduction of elevated left ventricular filling pressure in cardiac failure by oral, long-acting nitrate therapy. Presented at The American Federation for Clinical Research, San Francisco, Calif, April 29-May 1, 1978.

Please see following page for brief summary of prescribing information.

Conclusions

1. The prolonged reduction in preload and afterload reduces the amount of energy expended and oxygen consumed by the heart. This reduction in oxygen demand should relieve or prevent angina.
2. Provides a smooth onset of action without tachycardia. Unwanted effects are rare, and patient compliance is excellent.

PERITRATE® 40 mg
(pentaerythritol tetranitrate)

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Peritrate® SA
Sustained Action
(pentaerythritol tetranitrate) **80 mg**
Peritrate®
(pentaerythritol tetranitrate) **40 mg**
Peritrate®
(pentaerythritol tetranitrate) **20 mg**
Peritrate®
(pentaerythritol tetranitrate) **10 mg**

CAUTION: Federal law prohibits dispensing without prescription.
Description: Each tablet of Peritrate SA Sustained Action contains: pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Each tablet of Peritrate 40 mg contains pentaerythritol tetranitrate 40 mg. Each tablet of Peritrate 20 mg contains pentaerythritol tetranitrate 20 mg. Each tablet of Peritrate 10 mg contains pentaerythritol tetranitrate 10 mg. Peritrate (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg and Peritrate (pentaerythritol tetranitrate) are contraindicated in patients who have a history of sensitivity to the drug.
Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.
Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.
Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe, persistent headaches may occur.

In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:

(a) Cutaneous vasodilatation with flushing.
(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.
(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

Dosage: Peritrate (pentaerythritol tetranitrate) may be administered in individualized doses up to 160 mg a day. Dosage can be initiated at one 10 mg or 20 mg tablet q.i.d. and titrated upward to 40 mg (two 20 mg tablets or one 40 mg tablet) q.i.d. one-half hour before or one hour after meals and at bedtime. Alternatively, Peritrate Sustained Action 80 mg can be administered on a convenient b.i.d. dosage schedule.
Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg—double-layer, biconvex, dark green/light green tablets in bottles of 100 (N 0047-0004-51) and 1000 (N 0047-0004-60). Also unit dose, package of 10 x 10 strips (N 0047-0004-11).

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Peritrate (pentaerythritol tetranitrate) 10 mg—light green, unscored tablets in bottles of 100 (N 0047-0007-51) and 1000 (N 0047-0007-60).
STORE BETWEEN 59° and 86° F (15° and 30° C).
Animal Pharmacology: In a series of carefully designed studies in pigs, Peritrate (pentaerythritol tetranitrate) was administered for 48 hours before an artifically induced occlusion of a major coronary artery and for seven days thereafter. The pigs were sacrificed at various intervals for periods up to six weeks. The result showed a significantly larger number of survivors in the drug-treated group. Damage to myocardial tissue in the drug-treated survivors was less extensive than in the untreated group. Studies in dogs subjected to oligemic shock through progressive bleeding have demonstrated that Peritrate (pentaerythritol tetranitrate) is vasoactive at the postarteriolar level, producing increased blood flow and better tissue perfusion. These animal experiments cannot be translated to the drug's actions in humans.
Full information is available on request.

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Systemic Hypertension Complicating Tetralogy of Fallot: Effects of Antihypertensive Therapy

WILLIAM BENGE, MD
CARL W. WHITE, MD, FACC*

Iowa City, Iowa

A 20 year old woman with tetralogy of Fallot and an associated atrial septal defect presented with severe hypertension and congestive heart failure. She had been acyanotic for several years. An acute trial of antihypertensive therapy during cardiac catheterization resulted in severe systemic oxygen desaturation and loss of consciousness. Since surgical correction, antihypertensive therapy has been well tolerated. This case demonstrates the hemodynamic importance of systemic vascular resistance in tetralogy of Fallot and the need for extreme caution if aggressive antihypertensive therapy is attempted before surgical correction.

Congestive heart failure is frequent in tetralogy of Fallot in adults,[1] although it is rare in children.[2] When present it can be a manifestation of systemic hypertension.[3] The following case illustrates the hemodynamic contribution of increased systemic vascular resistance in producing a striking absence of cyanosis and associated physical findings, and emphasizes the hazard of antihypertensive therapy before surgical correction.

Case Report

A 20 year old retarded white woman first presented to the University of Iowa Hospitals at age 2 1/2 years with a congenital heart murmur associated with episodes of cyanosis, squatting and occasional loss of consciousness. Additional problems included a partial cleft palate, congenital dislocation of the hip, difficulties in eating, a lack of intellectual development and strabismus with bilateral eyelid ptosis. Examination revealed a high arched palate with a submucosal cleft defect and a bifid uvula. A systolic thrill, palpable throughout the precordium, was associated with a grade 5/6 systolic murmur that was most audible at the base of the precordium. No pulmonary component of the second heart sound was heard. Slight cyanosis of the lips and nail beds was noted. Chest roentgenography disclosed mild cardiomegaly, right ventricular enlargement and a right-sided aortic arch. Electrocardiography revealed right ventricular hypertrophy.

When the patient returned at ages 5 and 6 years, the physical findings were the same except for an increase in right ventricular hypertrophy, as demonstrated on electrocardiography. Hemoglobin was 16.8 and 17.7 g/100 ml, respectively, at these visits. The patient was not seen again at the University Hospitals until 1976. In the interim she had been free of symptoms with no episodes of cyanosis, squatting or loss of consciousness during the preceding 5 years. In April 1976 she was seen by her personal physician for abdominal discomfort and dyspnea. During the preceding 2 or 3 days abdominal swelling, pedal edema and increasing dyspnea had developed. Examination revealed moist rales throughout the lungs, a grade 4/6 harsh systolic murmur obscuring other heart sounds, a severely distended abdomen with ascites, peripheral edema and mottling of the limbs. Chest roentgenography revealed marked pulmonary congestion. After she was treated for congestive failure with digitalis and diuretic agents, her condition improved.

From the Cardiovascular Center and Cardiovascular Division, Department of Internal Medicine, University of Iowa College of Medicine, Iowa City, Iowa. Manuscript received January 16, 1978; revised manuscript received March 8, 1978, accepted March 22, 1978.

* This work was done during the tenure of the author as an American Heart Association Teaching Scholar.

Address for reprints: Carl W. White, MD, Cardiovascular Division, University of Iowa Hospitals, Iowa City, Iowa 52242.

The patient was transferred to the University of Iowa Hospitals on April 30, 1976 for further evaluation. On admission, blood pressure was 165/120 mm Hg, pulse 80/min and respiration 20/min. There was no edema, cyanosis or jugular venous distension. The lungs were clear on auscultation. She had a prominent left hemithorax with a marked left parasternal impulse. The first heart sound was normal, the second was single and the third heart sound was of right ventricular origin. A grade 6/6 harsh systolic murmur was maximal at the second and third intercostal spaces near the left sternal border and was associated with a systolic thrill felt throughout the precordium. The liver and spleen were not palpable, and there was no ascites. Hemoglobin was 16.3 g/100 ml. Blood pressure was approximately 170/120 mm Hg throughout her hospi-

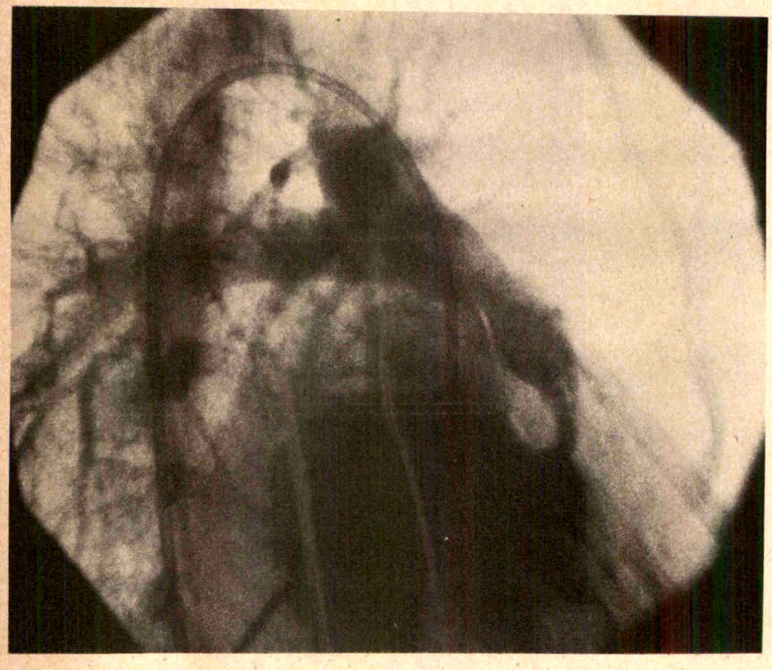

FIGURE 1. Right ventriculogram (right anterior oblique view) showing marked infundibular and valve stenosis of the ventricular outflow tract and the appearance of dye in the aorta.

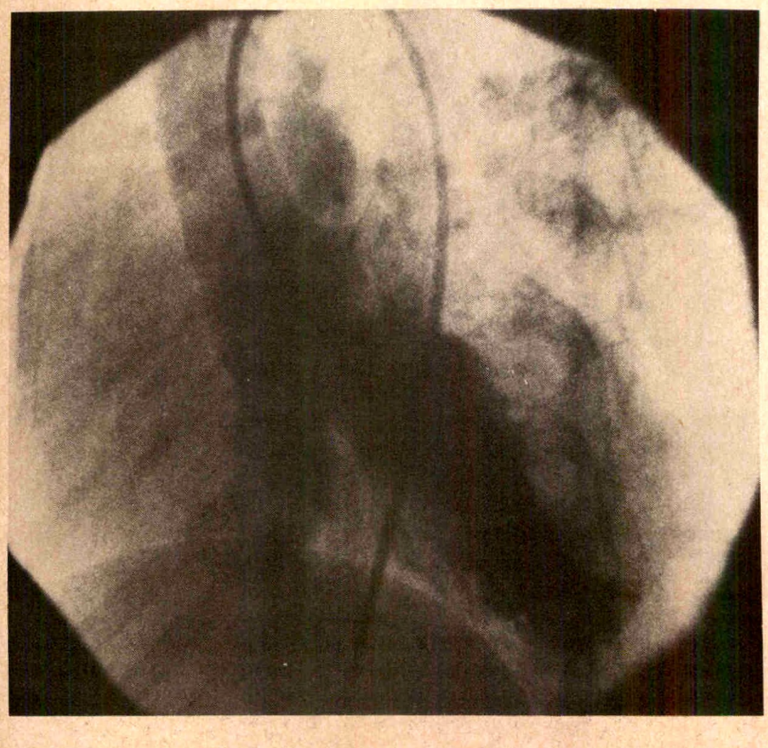

FIGURE 2. Left ventriculogram (left anterior oblique view) showing a large interventricular septal defect and overriding aorta.

TABLE I

Cardiac Catheterization Data

Pressures (mm Hg)	
Right ventriclular	170/12
Pulmonary arterial	30/7
Left ventricular	175/15
Aortic	175/120
Flows (liters/min)	
Cardiac output	1.8
Pulmonary flow	4.3
Left to right shunt	2.8
Right to left shunt	0.2
Resistances (dynes·sec·cm^{-5})	
Systemic	6237
Pulmonary arteriolar	226
Oxygen saturation (vol %)	
Mixed venous	10.8
Superior vena cava	10.0
Inferior vena cava	13.3
Right atrium	16.2
Right ventricle	16.7
Pulmonary artery	16.5
Left atrium	19.7
Left ventricle	19.7
Aorta	18.6

TABLE II

Nitroprusside Infusion

	Control		Nitroprusside*	
Site	Pressure (mm Hg)	O_2 Sat (%)	Pressure (mm Hg)	O_2 Sat (%)
Right ventricle	144/8	69	120/6	20
Aorta	156/96	86	120/70	34

* Rate of nitroprusside infusion was 30 μg/min.
O_2 Sat = oxygen saturation.

talization. The electrocardiogram revealed right axis deviation, right atrial enlargement and biventricular hypertrophy. The chest roentgenogram revealed marked cardiomegaly, prominent pulmonary vasculature and a right-sided aortic arch. The echocardiogram disclosed an overriding aorta and thickening of the interventricular septum, left ventricular posterior wall and right ventricular anterior wall.

Cardiac catheterization (Table I) revealed an atrial septal defect, a ventricular septal defect, infundibular and pulmonary valve stenosis, an overriding aorta with a right-sided aortic arch, and bidirectional shunting with predominant left to right shunting at the atrial level (Fig. 1 and 2). Because the patient was acyanotic and her symptoms resulted primarily from left ventricular failure, oral antihypertensive therapy was considered. However, before this therapeutic regimen was instituted, the patient was taken back to the catheterization laboratory for an acute trial of antihypertensive therapy. Nitroprusside, 30 μg/min, was infused intravenously for 5 minutes to lower the systemic pressure to the normal range (Table II). The patient suddenly lost consciousness and became severely cyanotic, requiring immediate discontinuation of the nitroprusside infusion. She regained consciousness within 1 minute and had no sequelae. It was apparent that surgical correction would be necessary before the initiation of any chronic antihypertensive therapy.

At operation, a right aortic arch, a 1.5 by 1.5 cm atrial septal defect, a 1.0 by 1.5 cm ventricular septal defect and combined infundibular and pulmonary valve stenosis were noted. Postoperatively the patient has been free of symptoms; she receives chlorthalidone, 100 mg daily, and maintains a blood pressure of about 140/90 mm Hg.

Comments

Major physiologic determinants of the hemodynamics in tetralogy of Fallot, with or without an associated atrial septal defect, are (1) the degree of right ventricular outflow obstruction, (2) the size of the ventricular septal defect, and (3) the systemic vascular resistance.[4,5] There have been few reports on patients with hypertension complicating tetralogy of Fallot. Of 25 adult patients with tetralogy described by Higgins and Mulder,[1] none had significant hypertension. Although half of the patients in their series were acyanotic, the absence of cyanosis was not the result of increased systemic vascular resistance. Rather, in these patients acyanosis was associated with a well developed bronchial collateral circulation that appeared to enhance long survival. Congestive heart failure occurred with equal frequency in both the acyanotic and cyanotic groups and was thought to be due to the volume overload of the left ventricle secondary to the compensatory systemic to pulmonary arterial shunting.

Effect of hypertension on cyanosis and prognosis in tetralogy: Our patient illustrates a less well known mechanism for the lack of cyanosis and the development of congestive heart failure in patients with tetralogy of Fallot, namely, severe systemic hypertension. The hemodynamic importance of increased systemic vascular resistance in preventing overt cyanosis in tetralogy is dramatically illustrated by the rapid occurrence of marked oxygen desaturation when blood pressure was lowered to the normal range. This therapy was attempted in this patient because her symptoms appeared to be primarily related to left ventricular failure. The sudden occurrence of cyanosis might not be surprising if one lowered blood pressure and systemic vascular resistance from normal to hypotensive levels. However, this patient demonstrates that severe oxygen desaturation can occur even when blood pressure is lowered from high to normal levels; her right ventricular and aortic pressures were never below 120 mm Hg.

Holladay and Witham,[3] describing "unusual" cases of tetralogy in 1957, noted hypertension in 12 of 22 patients in whom data on blood pressure were recorded. Somewhat surprising was the poor prognosis in this subgroup. Eight of the 10 deaths occurred in the hypertensive patients; six of the eight patients died of congestive heart failure. In one hypertensive patient severe oxygen desaturation developed when marked hypotension occurred during catheterization.

Effect of hypertension on intracardiac shunting: An associated atrial septal defect occurs in 10 to 40 percent of patients with tetralogy of Fallot.[6,7] Shunting in most reported cases of tetralogy is right to left across the atrial defect.[8] Our patient had a significant left to right shunt during the initial catheterization, probably because of the hypertension and elevated systemic vascular resistance. Moffitt et al.[9] also noted resting left

to right shunts that reversed direction during severe exertion in patients with an atrial septal defect and pulmonary stenosis.

Implications: This case illustrates that differences in the resistance to outflow in both the right and left ventricles are important in determining the direction and magnitude of intracardiac shunting in tetralogy of Fallot. In patients with this syndrome and systemic hypertension, attempts to lower blood pressure to the normal range may be hazardous.

It is not known whether other antihypertensive drugs would act similarly to nitroprusside if administered to patients with tetralogy of Fallot. The magnitude of desaturation with only modest reductions in arterial pressure suggests that extreme caution is necessary if aggressive antihypertensive therapy is initiated before surgical correction of this lesion.

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References

1. **Higgins CB, Mulder DB:** Tetralogy of Fallot in the adult. Am J Cardiol 29:837–846, 1972
2. **Hurst JW, Spanns JF:** Etiology and clinical recognition of heart failure. In, The Heart (Hurst JW, Logue RB, ed). New York, McGraw-Hill, 1974, p 446
3. **Holladay WE Jr, Witham AC:** The tetralogy of Fallot: the variability of its clinical manifestations. Arch Intern Med 100:400–413, 1957
4. **Perloff JK:** The Clinical Recognition of Congenital Heart Disease. Philadelphia, WB Saunders, 1970, p 356, 357
5. **Rudolph AM:** Right ventricular outflow obstruction with ventricular septal defect. In, Paediatric Cardiology, chap 39 (Watson H, ed). Saint Louis, CV Mosby, 1968, p 556–575
6. **Ikeda M, Hirosawa K:** Tetralogy of Fallot. Circulation 38:Suppl V: V-21–V-34, 1968
7. **Brinton WD, Campbell M:** Necropsies in some congenital diseases of the heart, mainly Fallot's tetralogy. Br Heart J 15:335–349, 1953
8. **Hudson REB:** Congenital pulmonary stenosis and atresia; anomalies of the pulmonary arteries. In, Cardiovascular Pathology (Hudson REB, ed), chap 41. Baltimore, Williams & Wilkins, 1965, p 1904
9. **Moffitt GR, Zimmer HF, Kuo PT, et al:** Pulmonary stenosis with left to right intracardiac shunts. Am J Med 16:521–527, 1954

Shunt Flow and Pulmonary Hemodynamics During Labor and Delivery in the Eisenmenger Syndrome

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The Eisenmenger syndrome carries a high mortality rate in women during delivery and the immediate postpartum period. It has been suggested that marked changes in shunt flow and pulmonary hemodynamics may be responsible. These functions were studied under various physiologic and pharmacologic conditions during labor and delivery in a patient with the Eisenmenger syndrome. Uterine contractions were associated with a decrease in the ratio of pulmonary to systemic blood flow (Qp/Qs) from 1.58 to 1.05. The Qp/Qs ratio also decreased (to 0.83) when forceps were applied during uterine contractions. Epidural anesthesia, oxytocin and the supine position did not adversely affect pulmonary hemodynamics or shunt flow. On the basis of these results, if pregnancy cannot be terminated in a patient with the Eisenmenger syndrome, it is recommended that the patient be given high concentrations of oxygen and epidural anesthesia and that serial arterial blood gas determinations be performed to detect changes in shunt flow.

The Eisenmenger syndrome or reaction[1] in pregnant women carries a high mortality rate during delivery and the immediate postpartum period.[2–5] The reason for the increased mortality is unknown, although it has been proposed that marked changes in shunt flow and pulmonary hemodynamics, with or without in situ pulmonary thrombi, may be responsible.[6] The effect of labor and uterine contractions on pulmonary hemodynamics in the Eisenmenger reaction is also unknown. We investigated hemodynamics and shunt flow during labor, delivery and the puerperium in a patient with the Eisenmenger syndrome. We also examined the effect on these functions of various medications commonly used during labor.

Case Report

A 28 year old woman was admitted to Mount Sinai Medical Center at 24 weeks of pregnancy for observation because of known heart disease. A heart murmur had been noted at birth. Cardiac catheterizations performed at ages 5, 13 and 17 years demonstrated a ventricular septal defect with an overriding aorta, pulmonary arterial pressure equal to systemic pressure and a bidirectional shunt on oximetry (Table I). A therapeutic abortion advised early in gestation had been refused by the patient. She had had nonprogressive dyspnea on exertion for many years. On admission, the patient was in no acute distress. She had a prominent pulmonary closure sound and right ventricular impulse, and a grade 1/6 systolic murmur along the left sternal border with radiation to the base. Mild digital clubbing was noted. Hemoglobin was 15.5 g/100 ml and arterial partial pressure of oxygen (PO_2) 59 mm Hg, with an oxygen saturation of 89 percent. Electrocardiography demonstrated right axis deviation and right ventricular hypertrophy (Fig. 1). Chest roentgenography revealed prominent pulmonary arteries and oligemic lung fields (Fig. 2). Echocardiography demonstrated a mitral and tricuspid valve without an interposed septum and a diminutive A wave in the pulmonary valve.

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During the hospitalization the patient experienced a mild but progressive increase in exertional dyspnea with no change in resting arterial oxygen saturation. She was treated with bed rest, intermittent oxygen therapy and heparin. During the 37th week of gestation she went into spontaneous labor. Heparin was discontinued, and a normal girl weighing 2.7 kg was delivered transvaginally with forceps under epidural anesthesia. The patient's postpartum course was uncomplicated.

TABLE I

Cardiac Catheterization Data in 1967 at Age 17 Years

Site	Pressure (mm Hg)*	Oxygen Saturation (%)
SVC	. . .	58
RA		
High		58.5
Mid	A = 7, V = 5 (5)	66.5
Low		67.5
IVC	. . .	66.5
RV		
Mid		81.0, 83.5
Apex	110/8	86.5
MPA		
Proximal	110/55 (81)	79.0, 77.0
Distal	99/45 (72)	79.5
LV		
Outflow	110/8	88.0, 93.0
Apex	110/7	90.0
Aorta	106/73 (89)	92.0
Femoral artery	. . .	91.0
	Qp/Qs = 2.2/1	

* Numbers in parentheses are mean pressures.
IVC = inferior vena cava; LV = left ventricle; MPA = main pulmonary artery; Qp/Qs = ratio of pulmonary to systemic blood flow; RA = right atrium; RV = right ventricle; SVC = superior vena cava.

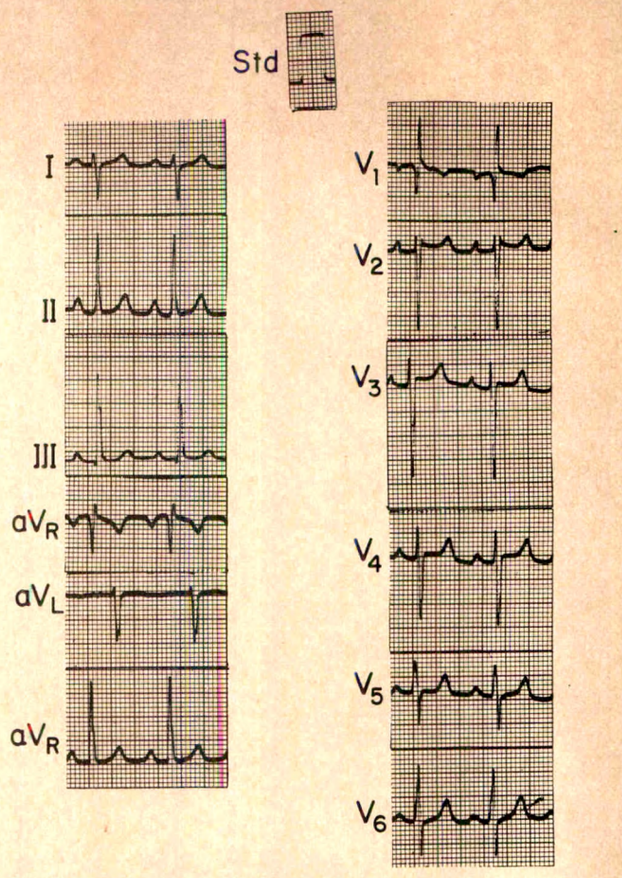

FIGURE 1. Electrocardiogram demonstrating right axis deviation and right ventricular hypertrophy. std = standardization.

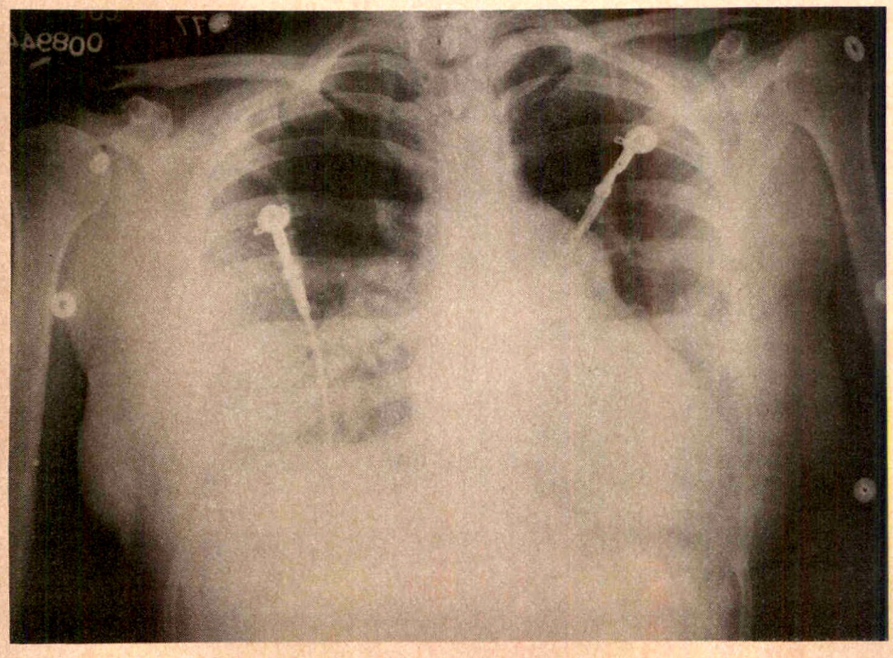

FIGURE 2. Chest roentgenogram (antero-posterior view, sitting) showing prominent central pulmonary arteries and relatively oligemic peripheral lung fields.

Methods

Informed consent was obtained for all instrumentation, in compliance with Mount Sinai Medical Center procedure. With the onset of spontaneous labor, an arterial cannula was placed percutaneously into the right radial artery, and a balloon-tipped flotation catheter was directed into the pulmonary artery under pressure monitoring. Pressure measurements and blood samples were obtained from the radial artery, pulmonary artery and right atrium. Antibiotic prophylactic therapy for vaginal delivery consisting of intravenous cephalothin (2 g every 6 hours) and gentamicin (4 mg/kg per day in divided doses) was administered; the patient was allergic to penicillin. Serial blood samples were obtained in heparinized syringes for analysis in an ABL-1 acid-base laboratory (Radiometer, Copenhagen). Blood gases (pH, partial pressure of carbon dioxide [pCO_2] and PO_2) were determined and oxygen saturation was calculated. Because of the nature of labor and delivery, it was not technically feasible to collect expired air to determine oxygen consumption and cardiac output. The pulmonary arterial catheter was removed 3 hours after delivery; a second catheter was inserted 1 day postpartum, using fluoroscopy, and repeat measurements were obtained.

Measurements were performed to determine the following: right atrial, pulmonary arterial and systemic arterial pressure; right atrial (MVO_2), pulmonary arterial (PAO_2) and systemic arterial (SAO_2) oxygen content; systemic arterial partial pressure of CO_2 (PCO_2); arteriovenous oxygen difference; and the ratio of pulmonary to systemic blood flow (Qp/Qs). These determinations were performed between uterine contractions and at the onset of labor at different inspired oxygen concentrations (FIO_2). Inspired oxygen concentration was kept constant, and these values were determined during labor in the supine and lateral decubitus positions, with oxytocin administration, with uterine contractions, during delivery with

TABLE II

Hemodynamic and Oximetric Data and Qp/Qs Ratio

	1 Room Air: Supine	2 40% FIO_2: Supine	3 80% FIO_2: Supine	4 80% FIO_2: Lateral Decubitus, Oxytocin	5 80% FIO_2: Supine, Oxytocin	6 80% FIO_2: Supine, Contraction, Oxytocin
Arterial pressure (mm Hg)	136/63 (80)	132/59 (80)	133/64 (81)	130/60 (79)	135/60 (80)	151/66 (88)
Pulmonary pressure (mm Hg)	120/50 (79)	103/37 (68)	104/40 (67)	106/45 (72)	108/40 (70)	127/38 (78)
Arterial O_2 sat (%)	90.5	94.5	96.2	96.0	96.2	92.8
Pulmonary O_2 sat (%)	82.1	85.4	87.2	86.5	87.8	82.1
Right atrial O_2 sat (%)	75.2	78.1	79.1	77.9	79.4	77.4
Qp/Qs						
PVO_2 = 95%*	1.18	1.70	2.19	. . .	. . .	. . .
PVO_2 = 98%*	0.96	1.30	1.58	1.57	1.65	0.97
PVO_2 = 100%*	0.85	1.12	1.34	. . .	. . .	. . .
Arteriovenous O_2 diff. (vol. %)	3.18	3.40	3.55	3.86	3.49	3.19

	7 80% FIO_2: Supine, Contraction, Oxytocin	8 80% FIO_2: Supine, Epidural, Oxytocin	9 80% FIO_2: Supine, Contraction, Oxytocin, Forceps	10 80% FIO_2: Supine, 1 hr Postpartum	11 Room Air Supine, 1 Day Postpartum	12 80% FIO_2: Supine, 1 Day Postpartum
Arterial pressure (mm Hg)	146/60 (87)	135/62 (80)	. . .	123/56 (78)	110/57 (70)	110/55 (70)
Pulmonary pressure (mm Hg)	122/35 (75)	112/30 (70)	120/50 (80)	103/65 (81)	104/38 (67)	95/35 (62)
Arterial O_2 sat (%)	90.5	95.8	88.9	93.3	91.8	94.9
Pulmonary O_2 sat (%)	80.6	86.0	78.1	91.9	82.8	88.9
Right atrial O_2 sat (%)	70.8	76.9	72.3	83.5	75.5	79.65
Qp/Qs						
PVO_2 = 95%*	. . .	. . .	. . .	. . .	1.34	2.50
PVO_2 = 98%*	1.13	1.57	0.83	1.61	1.07	1.68
PVO_2 = 100%*	. . .	. . .	. . .	. . .	0.95	1.37
Arteriovenous O_2 diff. (vol. %)	3.49	3.92	3.45	2.04	2.96	2.86

* Assumed value used to calculate Qp/Qs ratio.

diff = difference; FIO_2 = inspired oxygen concentration; PVO_2 = pulmonary venous oxygen saturation; Qp/Qs = ratio of pulmonary to systemic blood flow; sat = saturation; vol % = volumes percent.

epidural anesthesia and immediately and 1 day postpartum.

The ratio of pulmonary to systemic blood flow was calculated from the following[7]:

$$Qp/Qs = SAO_2 - MVO_2/PVO_2 - PAO_2$$

where PVO_2 is assumed pulmonary venous oxygen content. Pulmonary venous oxygen saturation was assumed to equal 98 percent when inspired oxygen concentration was approximately 0.8.[8] However, Qp/Qs was also calculated with assumed values of 95 and 100 percent to determine the effect on the Qp/Qs ratio of changes in FIO_2, because small changes in pulmonary venous oxygen content may markedly change the Qp/Qs value.

Results

Control: Baseline data, at the beginning of labor and between uterine contractions, confirmed the presence of marked pulmonary hypertension with a pulmonary arterial pressure of 120/50 (mean 67) mm Hg. Pullback from the pulmonary artery to the right ventricle failed to demonstrate a pressure gradient, and right atrial pressure was normal. Phasic increases in pressure were observed in both the systemic and the pulmonary circulations with each uterine contraction; this finding has also been reported in normal subjects.[9] In addition, a patient with the Eisenmenger reaction in association with an atrial septal defect was reported[10] to have an increase in right ventricular pressure compared with the level at 1 hour postpartum (based on two isolated measurements), but no mention was made of whether the reading was associated with an active uterine contraction.

Varying inspired oxygen concentrations: Table II lists, in chronologic order, data obtained during the spontaneous physiologic changes of labor and with pharmacologic interventions. Determinations 1, 2 and 3 were obtained when the inspired oxygen concentration (FIO_2) was varied at the beginning of labor between uterine contractions. Pulmonary arterial pressure decreased from a mean of 79 to 67 mm Hg when FIO_2 was increased from approximately 0.2 (room air) to 0.8 (100 percent oxygen administered with a face mask with an oxygen reservoir)[11]; during this time systemic arterial pressure remained constant at a mean of 80 mm Hg. The arteriovenous oxygen difference of 3 to 3.5 volumes percent indicated a high cardiac output, which is found in normal subjects during labor.[12] The Qp/Qs ratio, at an assumed pulmonary venous O_2 saturation of 98 percent, increased from 0.96 to 1.58 when FIO_2 was increased. The decrease in pulmonary arterial pressure and improvement in the Qp/Qs ratio suggests that there was a component of reactivity in the patient's pulmonary arteriolar circulation. For the remainder of labor, FIO_2 was maintained at approximately 0.8.

Active uterine contractions: Determination 5, made during the administration of oxytocin, a uterine smooth muscle stimulant, shows that between contractions oxytocin caused no important change in Qp/Qs ratio, arterial pressure or arteriovenous oxygen difference, compared with control values. Determination 4 was made to determine whether assumption of the lateral decubitus position alters hemodynamics. Again, no significant change was observed. Determinations 6 and 7 were obtained during active uterine contractions and showed an elevation of both systemic and pulmonary pressures and a marked decrease in the Qp/Qs ratio compared with control values. Mean systemic arterial pressure increased from 81 to 88 mm Hg and mean pulmonary arterial pressure from 67 to 77 mm Hg; the Qp/Qs ratio decreased from 1.58 to 1.05. Arterial oxygen saturation decreased from 96 to 91.7 percent, but arterial pCO_2 remained relatively constant; thus the decrease in arterial saturation was not caused by hypoventilation. Determination 9 was made during active uterine contractions and concomitant application of forceps. Results were similar to those obtained during uterine contractions without forceps; pulmonary arterial pressure increased to a mean of 80 mm Hg, the Qp/Qs ratio decreased to 0.83. Thus the application of forceps showed little hemodynamic effect above that of uterine contraction alone.

Epidural anesthesia: Determination 8 was made after the introduction of epidural anesthesia without epinephrine (chloroprocaine hydrochloride, 4 ml of 2 percent solution; no important change was noted in arterial pressure, Qp/Qs ratio or arteriovenous oxygen difference. Determination 10 was made 1 hour postpartum; no important difference from control was noted.

Postpartum: Determinations 11 and 12, the last two sets in Table II, were made at 1 day postpartum at inspired oxygen concentrations of 0.2 and 0.8. At a concentration of 0.8 (determination 12), the Qp/Qs ratio was unchanged from that during labor; however, both systemic and pulmonary arterial pressures were lower. When inspired oxygen concentration was 0.2, the Qp/Qs ratio was again unchanged; however, systemic and pulmonary arterial pressures were again lower compared with a similar determination during labor. Pulmonary arterial pressure decreased with increasing inspired oxygen concentration from a mean pressure of 67 to 62 mm Hg, but systemic pressure remained constant; these results are similar to those obtained during labor. The Qp/Qs ratio increased, as in determinations 1 to 3, from a baseline value of 1.07 to 1.68 with increasing inspired oxygen concentration.

Discussion

In this study we examined the effects of uterine contractions, variations in inspired oxygen concentration, subject position and pharmacologic interventions on pulmonary and systemic hemodynamics and shunt flow in a patient with Eisenmenger's syndrome during labor and delivery. Increasing inspired oxygen concentration in our patient produced repeated mild decreases in pulmonary arterial pressure and an increase in the ratio of pulmonary to systemic blood flow (Qp/Qs), suggesting augmented flow through the lungs and a degree of pulmonary vascular reactivity to oxygen, which is a pulmonary vasodilator. Patients with the Eisenmenger reaction usually have a relatively fixed pulmonary vascular resistance, as determined with the administration of both oxygen and tolazoline.[13] During pregnancy systemic vascular resistance decreases, possibly as a result of hormonal factors,[14] and these factors may cause some changes in the pulmonary vascular bed that may be more easily detected in patients with a high pulmonary arterial pressure. Although for the reasons noted it may be difficult to calculate the changes in the Qp/Qs ratio because of the use of an assumed rather than a determined pulmonary venous oxygen concentration, the decrease in pulmonary arterial pressure in our patient at a high level of inspired oxygen concentration was clear and reproducible. Because the patient has not returned for further study we could not determine if reactive pulmonary vasculature was also present in the nonpregnant state.

Effects of uterine contraction and body position: Each determination performed during a uterine con-

traction demonstrated a substantial decrease in the ratio of pulmonary to systemic blood flow (Qp/Qs), with a concomitant increase in pressure in both arterial beds. The reason for this decrease in the Qp/Qs ratio may be related to the relative compliance of the pulmonary and systemic circulations. It has been shown that in patients without heart disease each uterine contraction causes an increase in cardiac output and right atrial and ventricular pressures.[15] If the pulmonary circulation was only slightly reactive in our patient and had a relatively fixed resistance compared with that of the systemic circulation, it would not be able to accommodate the augmented cardiac output associated with each uterine contraction. This condition would explain a tendency toward right to left shunting at the ventricular level. Such shunting is augmented by the low baseline systemic vascular resistance that occurs in pregnancy.[9]

One factor influencing cardiovascular status in late pregnancy and during labor is that the gravid uterus decreases cardiac output in the supine position, presumably by impeding venous return as a result of compression of the inferior vena cava.[15] In our patient we did not observe hemodynamic or shunt flow changes related to position.

Effect of anesthesia: There is concern about which method of anesthesia is safest in a patient with the Eisenmenger reaction[16] during labor. The hemodynamic effects of various forms of anesthesia in normal subjects have been studied,[17] but whether these findings can be extrapolated to the patient with the Eisenmenger reaction is questionable. In our study, a carefully administered epidural block (chloroprocaine hydrochloride 4 ml, 2 percent) caused no change in or adverse affect on pulmonary hemodynamics or shunt flow, thus supporting the use of this method of anesthesia. Oxytocin, a uterine smooth muscle stimulant, also had no adverse effect on hemodynamics or shunt flow in our patient and thus may be administered to patients with the Eisenmenger reaction.

Clinical implications: The patient who underwent this study was advised to undergo further evaluation but so far has not returned for follow-up care. Although our patient tolerated labor and delivery extremely well and without complication, we continue to advise therapeutic abortion in similar clinical situations, on the basis of the experience of others. When an elective abortion cannot be performed or a patient with the Eisenmenger reaction undergoes a similar stressful procedure such as tubal ligation, we recommend the administration of high concentrations of oxygen, epidural anesthesia and the determination of serial arterial blood gases to detect changes in shunt flow.

References

1. **Wood P:** The Eisenmenger syndrome. Br Med J 2:701–755, 1958
2. **Jones AM, Howitt G:** Eisenmenger syndrome in pregnancy. Br Med J 1:1627–1631, 1965
3. **Neilson G, Galea EG, Blunt A:** Eisenmenger's syndrome and pregnancy. Med J Aust 1:431–434, 1971
4. **Crawford JS, Mills WG, Pentecost BL:** A pregnant patient with Eisenmenger's syndrome. Br J Anaesth 43:1091–1094, 1971
5. **Pitts JA, Crosby WM, Basta LL:** Eisenmenger's syndrome in pregnancy. Am Heart J 93:321–326, 1977
6. **Naeye RL, Hagstrom JWL, Talmadge BA:** Postpartum death with maternal congenital heart disease. Circulation 36:3–4, 1967
7. **Yang SS, Bentivoglio LG, Maranhao V, et al:** From Cardiac Catheterization Data to Hemodynamic Parameters. Philadelphia, FA Davis, 1972, p 144
8. **Nadas AS, Fyler DC:** Pediatric Cardiology. Philadelphia, WB Saunders, 1972, p 526
9. **Metcalfe J, Ueland K:** Maternal cardiovascular adjustments to pregnancy. Prog Cardiovasc Dis 16:363–377, 1974
10. **Arias F:** Maternal death in a patient with Eisenmenger's syndrome. Obstet Gynecol 50:76s–80s, 1977
11. **Belinkoff S:** Introduction to Respiratory Care, second edition. Boston, Little, Brown, 1977, p 85
12. **Ueland K, Novy MJ, Peterson EW, et al:** Maternal cardiovascular dynamics. IV. The influence of gestational age on the maternal cardiovascular response to posture and exercise. Am J Obstet Gynecol 104:856–863, 1969
13. **Hallidie-Smith KA, Goodwin JF:** The Eisenmenger syndrome. Prog Cardiol 3:211–225, 1974
14. **Ueland K, Parer JT:** Effects of estrogens on the cardiovascular system of the ewe. Am J Obstet Gynecol 96:400–406, 1966
15. **Kerr MG:** Cardiovascular dynamics in pregnancy and labor. Br Med Bull 1:19–24, 1968
16. **Asling JH, Fung DL:** Epidural anesthesia in Eisenmenger's syndrome: a case report. Anes Anal 53:965–968, 1974
17. **Ueland K, Akamatsu TJ, Der Yuen D:** Maternal cardiovascular dynamics. VI. Cesarian section with epidural anesthesia without epinephrine. Am J Gynecol 114:775–784, 1972

Effect of Propranolol on Fetal Tachycardia In Diabetic Pregnancy

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Propranolol was administered during the last 20 days of pregnancy to a diabetic woman because of fetal tachycardia (heart rate approximately 200 beats/min). With a daily dose of 160 mg of propranolol, a fetal heart rate of 120 to 160 beats/min could be achieved. Blood concentration of propranolol was measured in the mother and infant after birth. The level in the neonatal blood was 20 percent of the maternal sample, which is definitely higher than expected from animal experiments. No undesirable effect of propranolol treatment was detected. Postpartum, the infant demonstrated paroxysmal supraventricular tachycardia, and propranolol was again essential in maintaining a normal rate.

Beta receptor blocking agents are being used with increased frequency in young patients with hypertension,[1] thyrotoxicosis,[2] obstructive cardiomyopathy[3] and paroxysmal atrial tachycardia,[4] but to date they have been used rarely to treat such fetal abnormalities as cardiac arrhythmia.[5] Indeed only a few cases of the use of propranolol during pregnancy have been reported.[1–14] The measurement of fetal serum propranolol levels has been reported in several cases.[12–14]

This report concerns the use of propranolol to treat tachycardia first recognized in the 35th week of pregnancy in the fetus of a diabetic woman. Propranolol levels were determined in the mother and infant at the time of cesarean section.

Case Report

This was the third pregnancy of a 35 year old woman with insulin-dependent diabetes of 3 years' duration. The first pregnancy was uneventful and occurred 3 years before the diagnosis of diabetes. Diabetes was diagnosed during the second pregnancy, which ended in a spontaneous abortion in the 3rd month. Subsequently the patient was treated with diet and insulin. The disease was labile, requiring daily administration of 4 units of regular insulin and 14 units of insulin-zinc suspension.

In her third pregnancy the woman required multiple daily doses of insulin in her 2nd month, the total dose reaching 86 units with the aim of keeping the blood sugar level at 100 mg/100 ml. There were repeated episodes of moderate hypoglycemia during the first trimester but no signs of ketosis. The patient was admitted to the Lindenhofspital in Berne at the end of the 34th week of pregnancy with hydramnios. At that time she weighed 68 kg and her blood pressure was 119/70 mm Hg. There were signs of marked hydramnios and 1+ peripheral edema.

The fetal status was monitored with seven human placental lactogen determinations; values ranged from 10.2 to 11.5 μg/ml, all higher than normal for our laboratory. At the end of the 36th week the amniotic fluid lecithin/sphingomyelin ratio was interpreted as demonstrating premature lung development. A second determination in the 37th week was judged normal.

The fetal heart rate at hospitalization was 200 beats/min (Fig. 1A). On three office visits before admission the rate had been 172, 144 and 200 beats/min, respectively. Administration of propranolol was begun on the 5th hospital day at 10 mg every 4 hours and increased to 40 mg every 6 hours. The fetal heart rate decreased to rates as low as 120 beats/min (Fig. 1B). The maternal heart rate

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also decreased from more than 100 beats/min in the 35th week to a range of 84 to 96 beats/min. The duration of treatment was 20 days.

Cesarean section was performed in the 37th week. Propranolol and blood glucose determinations were performed every 2 hours from midnight to the time of operation (Table I). The concentration of propranolol in the neonatal blood at the time of delivery was equal to 20.8 percent of the concentration found in the maternal blood. Unchanged propranolol was determined by gas chromatography with the beta blocking drug metoprolol (Lopresor®) as the internal standard.[15] The limit of detectability of the method used is approximately 10 ng/ml.

The fetal heart rate during the cesarean section was 140 beats/min. Marked hydramnios was found, and the fluid was meconium-stained. The female baby weighed 3,670 g and was delivered after 3 minutes with no apparent complications. The Agpar score was 7/9/9, the heart rate at delivery was 132 beats/min. The placenta weighed 630 g and showed several white infarctions up to 2.5 cm in diameter.

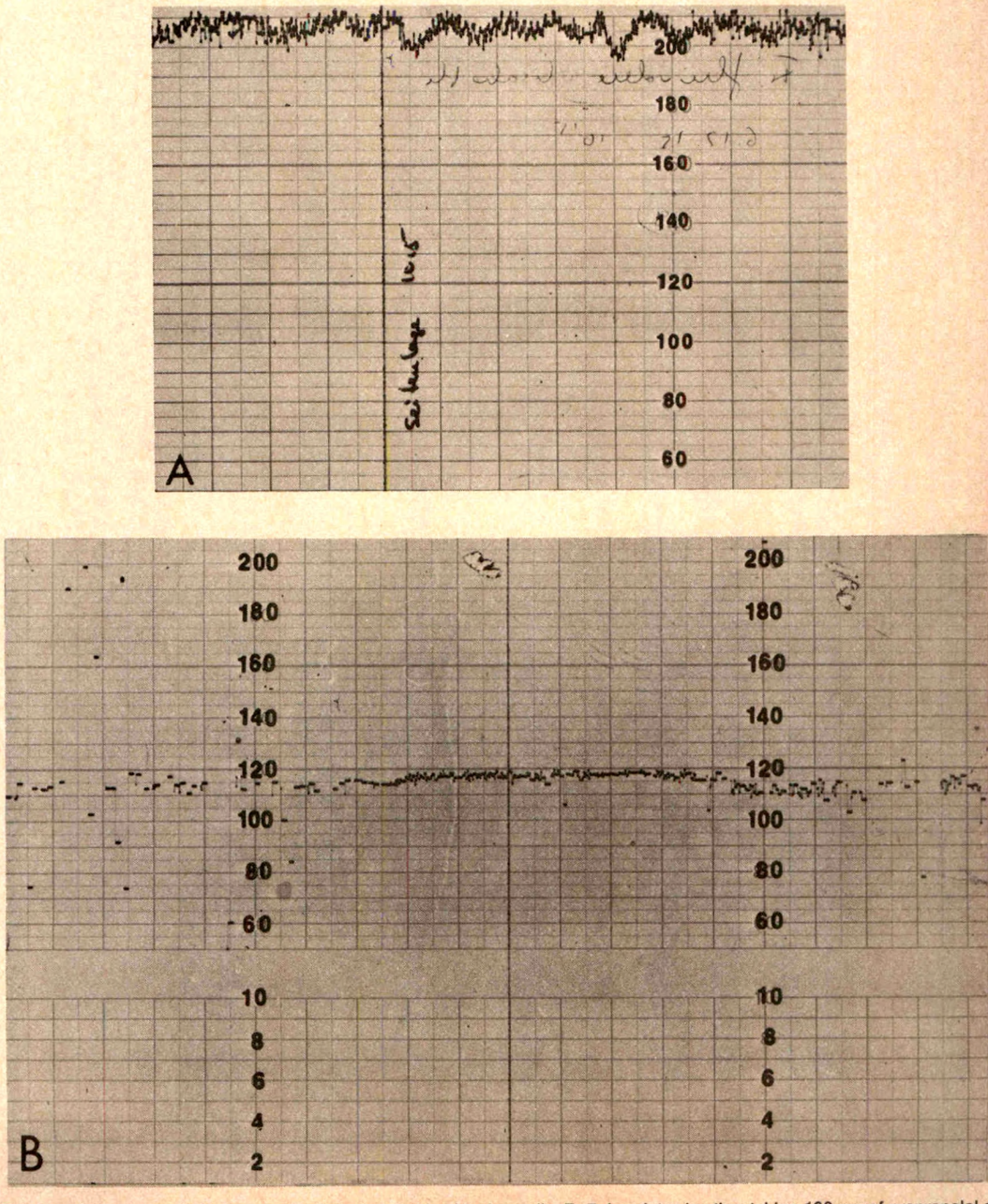

FIGURE 1. Fetal cardiotocogram. **A,** before medication, showing fetal tachycardia. **B,** 7 days later (mother taking 160 mg of propranolol daily) showing a decrease in fetal heart rate.

TABLE I

Glucose and Propranolol Determinations*

Time of Sample (hr)	Glucose (Venous Whole Blood)† (mg/100 ml)	Propranolol Concentration in Plasma (ng/ml)	
		Individual Determinations	Mean Value
	Mother		
00.00	100	70/68	69
02.00	103	111/116	114
04.00	112	90/91	91
06.00	132	113/117	115
07.55	*Cesarean Section; Glucose, 5% Intravenously*		
08.00	192	135/135	135
09.00	205	117/125	121
11.00	266	104/106	105
	Infant		
08.00	67	28/24	26
	Glucose, 10% Intravenously		
10.30	122‡	20/17	18.5
12.00	35§		
13.00	50§		
16.00	70§		

* Determinations performed at the Department of Pharmacology, CIBA-GEIGY, Basel, Switzerland.[13]
† Glucose-oxidase.
‡ Hexokinase.
§ Hexokinase, capillary whole blood.

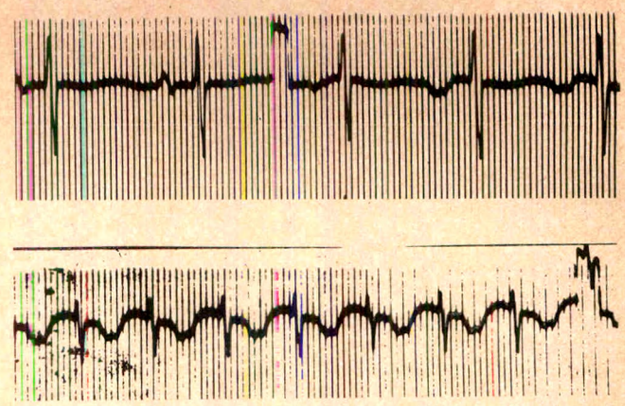

FIGURE 2. Infant electrocardiogram (precordial lead V_1). **Upper tracing,** on day 1, showing supraventricular rhythm (rate 120/min and 145/min), changing P wave axis and changing P-R interval (0.12 and 0.15 second). (Right axis deviation, atrial enlargement, right ventricular hypertrophy and ST-T changes, also found, are not shown.) **Lower tracing,** on day 3, showing supraventricular tachycardia (rate 250/min). In comparison with day 1, there is tachycardia, and the same P wave with slight prolongation of the corresponding P-R interval. (Right axis deviation, atrial enlargement, right ventricular hypertrophy as well as ST-T changes were also still present.) (In both tracings, paper speed is 50 mm/sec.)

Respiratory distress due to aspiration occurred within 15 minutes after delivery. This was treated with oxygen for 130 hours with a maximal concentration of 60 percent. No continuous positive airway pressure or ventilation was necessary. Hypoglycemia did not develop. Thrombocytopenia (platelet count 40,000/mm^3) was noted at age 1 hour, but the count became normal within 1 week. Neurologically the baby appeared to be hyperirritable during the first 4 days.

The baby's heart rate remained normal (140 to 160 beats/min) during the first 2 postpartum days, but on day 3 tachycardia (heart rate 250 beats/min) was detected (Fig. 2). Cardiac catheterization on day 5 detected no cardiac malformations. Cineangiography revealed no intracardiac shunt but a slightly enlarged left ventricle with increased wall thickness. The infant was treated with digoxin but there were frequent recurrences of tachycardia during days 4 and 5; accordingly, administration of propranolol, 3 mg intravenously three times a day, was begun on day 6. Subsequently no tachycardia was observed. At age 2 months, paroxysmal supraventricular tachycardia recurred, and the infant was treated by increasing the propranolol to 4 mg three times a day. The child is now 2 years old and well without medication; her electrocardiogram is normal.

Discussion

Pharmacokinetics of propranolol during pregnancy: The ability of beta blocking agents to cross the placental barrier has been demonstrated in experiments on animals.[16–19] Beta blocking drugs with a high degree of liposolubility, such as propranolol and oxprenolol, pass through the placental membrane more easily than those with a low degree of liposolubility, such as sotalol.[18] Information on the pharmacokinetics of drugs in the fetus is scant and often restricted to single determinations of drug concentrations in maternal and neonatal blood sampled at the time of delivery. Because the uterine and placental blood flow is modified by contractions during normal labor, the degree of exposure and the response of the fetus to a drug may not be the same as during pregnancy.[20]

In our case, there seems little doubt that the propranolol concentration in the neonatal blood sample was one fifth of the maternal concentration because this value was verified by a second determination 2 1/2 hours later. This concentration is much higher than would have been expected from the values found in animals; the maximal concentration of propranolol in fetal lamb plasma was only 5 percent of that reached in the pregnant ewe after intravenous infusion of the drug in a dose of 1 mg/kg.[21] In man, however, the same ratio of 1 to 5 was also found by Langer et al.[14] Cottril et al.[13] found similar concentrations both in maternal blood and in blood from umbilical vessels. Animal[17,22] and human[9] studies show that deceleration of the fetal heart rate occurs with the administration of propranolol. The beta receptor blockade produced by propranolol and oxprenolol lasts two to three times as long in the fetus as in the mother animal.[18]

Propranolol therapy of tachycardia during pregnancy and after birth: Intrauterine tachycardia can induce severe cardiac insufficiency. Cases of congenital hydrops after fetal atrial flutter or paroxysmal tachycardia have been described.[23–26] Saint-Martin and Lugassy[25] describe 26 patients with this condition: 18 were digitalized, 3 died and the remaining 5 experienced reversion to normal sinus rhythm without treatment. Accordingly, it seemed appropriate to us to attempt to treat the fetal tachycardia. In our patient the fetal heart rate became normal after treatment with propranolol.

After birth, the infant demonstrated paroxysmal supraventricular tachycardia, possibly induced by an ectopic atrial pacemaker. Propranolol in addition to digoxin appeared to be essential to maintaining a normal heart rate. The fundamental cause of this tachycardia is unknown. Wolff-Parkinson-White syndrome was not found, and cardiac catheterization and cineangiography excluded congenital malformations. However, some type of cardiomyopathy[27] cannot be excluded, especially in view of the angiographic finding of increased wall thickness of the left ventricle.

Side effects: None of the side effects described with prolonged use of propranolol in pregnancy[6–8,12,13] were found in the infant. The placenta and the baby were of normal weight. The Agpar score was normal. Hypoglycemia did not develop with prophylactic glucose infusion. No polycythemia was noted. The amniotic fluid was meconium-stained, as described in other cases in which propranolol was used.[7,11] However, it is not known whether this is a sign of intrauterine hypoxia or the consequence of the direct effect of propranolol on peristalsis. The fetal thrombocytopenia is unexplained and has not been described as a consequence of propranolol treatment.

Despite the lack of side effects of prenatal propranolol treatment in this child, this therapy cannot be dismissed as harmless. Its use must be weighed against the danger of development of fetal or neonatal cardiac insufficiency, or both.

Acknowledgment

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References

1. **Tscherdakoff Ph, Kreft C:** Traitement par le propranolol de l'hypertension artérielle chez la femme enceinte. Nouv Presse Med 6:629–632, 1977
2. **Bullock JL, Harris RE, Young R:** Treatment of thyrotoxicosis during pregnancy with propranolol. Am J Obstet Gynecol 121:242–245, 1975
3. **Turner GM, Oakley CM, Dixon HG:** Management of pregnancy complicated by hypertrophic obstructive cardiomyopathy. Br Med J 4:281–284, 1968
4. **Schroeder JS, Harrison DC:** Repeated cardioversion during pregnancy: treatment of refractory paroxysmal atrial tachycardia during three successive pregnancies. Am J Cardiol 27:445–446, 1971
5. **Eibschitz I, Abinader EG, Klein A, et al:** Intrauterine diagnosis and control of fetal ventricular arrhythmia during labor. Am J Obstet Gynecol 122:597–600, 1975
6. **Fiddler GI:** Propranolol and pregnancy. Lancet 2:722–723, 1976
7. **Gladstone GR, Hordorf A, Gersony WM:** Propranolol administration during pregnancy: effects on the fetus. J Pediatr 86:962–964, 1975
8. **Reed RL, Cheney CB, Fearon RE, et al:** Propranolol therapy throughout pregnancy, a case report. Anaesth Analg 53:214–218, 1974
9. **Renou P, Newman W, Wood C:** Automatic control of fetal heart rate. Am J Obstet Gynecol 105:949–953, 1969
10. **Mitrani A, Oettinger M, Abinader EG, et al:** Use of propranolol in dysfunctional labour. Br J Obstet Gynecol 82:651–655, 1975
11. **Tunstall ME:** The effect of propranolol on the onset of breathing at birth (abstr). Br J Anaesth 41:792, 1969
12. **Habib A, McCarthy JS:** Effects on the neonate of propranolol administered during pregnancy. J Pediatr 91:808–811, 1977
13. **Cottril CM, McAllister RG, Gettes L, et al:** Propranolol therapy during pregnancy, labor and delivery: evidence for transplacental drug transfer and impaired neonatal drug disposition. J Pediatr 91:812–814, 1977
14. **Langer A, Hung CT, McA'nulty JA, et al:** Adrenergic blockade. A new approach to hyperthyroidism during pregnancy. Obstet Gynecol 44:181–186, 1974
15. **Degen PH, Riess W:** Simplified method for the determination of oxprenolol and other β-receptor blocking agents in biological fluid by gas-liquid chromatography. J Chromatogr 121:72–75, 1976
16. **Van Petten GR, Willes RF:** Effect of some autonomic drugs on fetal cardiovascular function (abstr). Proc Can Fed Biol Soc 11:31, 1968
17. **Joelsson I, Barton MD:** The effect of blockade of the beta receptors of the sympathetic nervous system of the fetus. Acta Obstet Gynecol Scand 48:Suppl 3:75–79, 1969
18. **Truelove JF, Van Petten GR, Willes RF:** Action of several β-adrenoceptor blocking drugs in the pregnant sheep and fetus. Br J Pharmacol 47:161–171, 1973
19. **Van Petten GR:** Pharmacology and the fetus. Br Med Bull 31:75–79, 1975
20. **Krauer B, Krauer F:** Drug kinetics in pregnancy. Clin Pharmacokinetics 2:167–181, 1977
21. **Van Petten GR, Willes RF:** β-adrenoceptive responses in the unanesthetized ovine fetus. Br J Pharmacol 38:572–582, 1970
22. **Oakes GK, Walker AM, Ehrenkranz RA, et al:** Effect of propranolol infusion on the umbilical and uterine circulations of pregnant sheep. Am J Obstet Gynecol 126:1038–1042, 1976
23. **Cowan RH, Waldo AL, Harris HB, et al:** Neonatal paroxysmal supraventricular tachycardia with hydrops. Pediatrics 55:428–430, 1975
24. **Hedvall G:** Congenital paroxysmal tachycardia—a report of three cases. Acta Paediatr Scand 62:550–552, 1973
25. **Saint-Martin J, Lugassy G:** Tachycardies supraventriculaires du nouveau-né. A propos de deux observations avec anasarque foeto-placentaire. Pediatrie 30:419–428, 1975
26. **Silber DL, Durnin RE:** Intrauterine atrial tachycardia associated with massive edema in a newborn. Am J Dis Child 117:722–726, 1969
27. **Wolfe RR, Way GL:** Cardiomyopathies in infants of diabetic mothers. Johns Hopkins Med J 140:177–180, 1977

Value of Coronary Bypass Surgery

Controversies in Cardiology: Part I

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The value of coronary bypass surgery has been studied carefully during the last decade. Four methods, none perfect, have been used to compare the results of such surgery with the results of medical therapy. New data are likely to be merely supportive rather than the outcome of a definitive study with a new and acceptable experimental design. It is therefore time to analyze the available data in light of the treacherousness of the disease and to determine if a clear trend is evident. There appears to be sufficient evidence to state that properly performed coronary bypass surgery will increase coronary blood flow and relieve angina pectoris in 90 percent of patients; total relief of angina can be expected in 60 percent and partial relief in 30 percent. Compared with modern medical therapy, properly performed coronary bypass surgery appears to prolong the life of patients who have obstruction of the left main coronary artery or triple or double vessel disease. There is not adequate evidence to state that the procedure will prolong the life of patients with single vessel obstruction. However, patients with single vessel obstruction and unacceptable angina pectoris should be considered for bypass surgery (especially patients with obstruction of the left anterior descending coronary artery).

In practice, at Emory University Hospital, Atlanta, bypass surgery is recommended for young people with few symptoms if compelling obstructing lesions are present and in older patients only if their symptoms require it. Medical therapy is given before and after bypass surgery. When bypass surgery is performed in an excellent fashion (operative risk 1 percent) a great deal of "controversy" about this problem vanishes.

Coronary bypass surgery relieves angina pectoris and prolongs life in properly selected patients.[1] In this presentation we review the scientific data supporting this belief.

Methods of Scientific Study

Coronary atherosclerotic heart disease is an enigma. Because the disease is so poorly understood, one must expect difficulty in comparing one form of its treatment with another. Accordingly, there are no perfect studies. The four methods used to compare the long-term effect of coronary bypass surgery with medical treatment are as follows:

1. Retrospective matched studies. This method entails creating a study plan (protocol) and applying it to previously observed patients. For example, the effect of surgery performed during this decade can be compared with the effect of the medical treatment used during the last decade. There are two serious problems with this method: It is difficult to match the patients because of selection bias, and one cannot assume that the medical management used during the last decade has remained the same in this decade. In fact, there is evidence that medical management has improved during the last decade. Accordingly, if one did prove that surgical treatment performed in this decade was superior to medical treatment used in the last decade, it would have little relevance

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to modern patient care. Yet how certain are we that this approach has no value? The primary advantage of using this method is that many of the studies had angiographic documentation of the extent of the disease during an era when coronary bypass surgery was not performed. Therefore, all patients could be observed without the intervention of surgery and without the bias of selection for medical or surgical treatment.

Retrospective matched studies have been utilized when the surgical treatment and medical treatment were implemented during the same time period, but the problem of matching the patients with precision and without selection bias remains. With such studies, it is possible to diminish, but not to eliminate, the criticism that one of the types of treatment has improved during the last 5 to 10 years. For example, surgical treatment in many institutions is better now than it was 2 years ago.

2. Prospective matched studies. This method entails creating a study plan (protocol) and entering patients into the study as they are observed. Some patients will be entered into a surgical and some into a medical group. Selection bias may occur and influence the entry of patients into one or the other group. The difficulty in perfectly matching the two groups is always present. This method does eliminate some of the problems presented when all parts of a study are not carried out during the same time period. However, it does not guarantee that all of the variables are equalized. For example, in comparing the results of bypass surgery with those of medical management, one should use the same medical management in all patients in the medical group and use no medical treatment in the surgical group. This is obviously not possible.

3. Prospective randomized study.[2] Theoretically, this should be the best method of performing clinical trials. Practically, it often is not. Although all parts of the study are carried out during the same time period and patients are randomized, theoretically eliminating the problem of selection bias, not all variables are equally controlled. For example, there is a learning curve in bypass surgery. If the surgeons are just beginning their work at a given hospital, the surgical results will be poorer at the beginning than at the end of the study period, and the early results will favor the medically treated group. Second, experience has shown that it is impossible to retain patients in a medically treated group. Seventeen percent of the patients in the Veterans Administration clinical trial of patients with chronic stable angina and 33 percent of those in the National Institutes of Health clinical trial of patients with unstable angina "crossed over" from medical to surgical treatment (see later discussion). Such changes, of course, have profound influence on the interpretation of study results and make it impossible to draw firm conclusions regarding the long-term survival of either group. There is also the problem of the bias of the observer for or against surgery. The observer may advise a patient to go to a facility where he can be assured he will receive one or another form of therapy and does not enter certain patients into the study. When a prospective randomized study is carried out in numerous facilities, when a large number of people and procedures are involved and when the disease under study is as complex as atherosclerotic heart disease, it is impossible to control and match all of the variables involved. One hospital in a cooperative study might contribute 20 percent of the total number of patients and show that bypass surgery prolongs life by comparison with medical management. However, when these good surgical results are added to poorer surgical results of other hospitals in the study, the benefits of surgery may no longer be evident. To restate, prospective randomized clinical trials should give the best scientific results. To date, the trials that compare the medical and surgical treatment of coronary atherosclerotic heart disease have been difficult to implement and have been less than satisfactory.

4. Comparison of study groups with life tables. The Department of Health, Education, and Welfare has generated life tables that permit one to estimate the yearly survival rate of persons living in the United States. Various insurance companies have made similar tables. For example, if one knows the age, race and sex of a person one can predict his or her chances of surviving 5 years by referring to the life tables. Such tables give information regarding the annual death rate of the general population. The general population is made up of truly well people, apparently well people and sick people. The survival curve of patients will obviously be poorer than the survival curve of matched persons from the general population. Remember that the age, race and sex of the individual members of the study group must be matched with the age, race and sex of persons in the general population. The survival curves of study groups can be compared with the survival curves of persons from the general population (life table) and when the study groups are matched angiographically they can be compared with each other. This method of study is currently popular and has much merit. It, too, is not perfect. Some critics state that the number of patients in a study group is small when compared with the general population and that the former may not be a representative sample of the whole. We agree with this view but do not believe it a valid criticism because the objective is to see if an intervention can shift the survival curve for sick people toward the survival curve of people from the general population.

Comment: There is no perfect method of determining if coronary bypass surgery is superior to medical therapy in relieving angina pectoris or prolonging life. The first three methods mentioned have been utilized to compare the effect of bypass surgery and medical treatment in the relief of angina pectoris, and all four methods mentioned have been used to determine which mode of treatment (bypass surgery or medical management) is most useful in prolonging life.

Because each method of study has certain advantages and disadvantages, it seems logical to examine the results generated by all of the methods and to ascertain if a trend is evident. If a significant number of the methods, imperfect as they are, indicate the same trend,

then a real effect is more likely to be present than if the trends are divergent.

Finally, it is unlikely that new prospective randomized studies comparing the effect of coronary bypass surgery with medical therapy will be initiated. The problems created by the studies in progress have blunted the enthusiasm for such an approach. Accordingly, we must make up our mind using the data we now have.

None of the available studies show that modern medical treatment is superior to bypass surgery in prolonging life. A few studies show that the two methods of treatment are of equal value, but the majority show the superiority of bypass surgery to medical treatment in prolonging life. (We have already alluded to the fact that patients who have bypass surgery also continue medical treatment.)

Brief Note Regarding Statistical Analysis

Statistics is a set of tools that can be used to help make good decisions on the basis of limited and variable information or data.[3] No good statistician will claim that statistical methods necessarily yield absolute truth; however, proper use of statistics can permit one to make a better decision than is possible when the decision is based on opinion alone.

Statistical manipulation does not yield absolute truth. There is no way to find absolute truth in science, which is why science is defined as the search for truth. Statistical methods can minimize but cannot eliminate errors. It is wise to remember that in statistics there are two types of errors.[3,4] A type I error is made when one assumes that a certain intervention has produced a certain effect whereas in reality the effect produced is due to chance. The pure scientist wishes to avoid this type of error and sets up his or her investigation to do that. A type II error is made when an observed event is considered to be due to chance whereas in reality it is due to a scientific intervention. When an investigator sets up an investigation to minimize a type I error, the likelihood of a type II error is increased (and vice versa). Other information is utilized to determine which type of error should be avoided. The significance level (α) determines the acceptable risk of a type I error. The lower the significance level (α) the more likely one is to make a type II error. For example, if one chooses a significance level (α) of 0.001 in an effort to avoid a type I error, one might overlook a valuable method of treatment (and make a type II error).

Too little attention is paid to these problems. For example, it may be wise to accept a significance level of 0.075 when comparing two types of treatment if one treatment is not very satisfactory and the consequence of missing a valuable new treatment is death. We should remember that coronary atherosclerotic heart disease is the leading cause of death in this country and that about half of the subjects who die of it die suddenly. The disease is common, it is serious and current treatment is unsatisfactory. It follows that if a new treatment can be employed with little risk, it would be wise to err on the side of avoiding a type II error as well as having moderate, but not total, assurance that a type I error is being avoided. In other words, at this time, what type of error should be avoided? We obviously do not want to recommend a treatment that is not valuable or overlook a treatment that is valuable. We believe that the data now available on treatment of atherosclerotic heart disease should be viewed in this context.

Relief of Angina Pectoris

Coronary bypass surgery relieves angina pectoris in symptomatic patients. In Mundth and Austen's review[5] of 10,000 patients from 16 centers operated on before 1971, symptomatic relief of angina pectoris was reported in 60 to 70 percent. In our surgical patients at Emory University Hospital in Atlanta, we find that 92 percent have relief of symptoms and 62 percent are free of angina pectoris.

The Veterans Administration trial of patients with stable angina pectoris[6] showed greater relief of symptoms in surgically treated than in medically treated patients. The investigators concluded:

> In summary, a systematic evaluation of the severity of angina pectoris in a large scale randomized study has revealed substantial improvement in symptoms with a decrease in daily medications used in patients who received surgical treatment compared to medically treated cohorts. The degree of improvement is related to graft patency but a placebo effect is probably also present.

The National Institutes of Health randomized trial study of patients with unstable angina pectoris[7] showed a significantly greater occurrence of class III and IV angina pectoris in the follow-up period in medically treated patients (45 percent) than in surgically treated patients (15 percent).

Relief of pain is closely related to vein patency.[5] Seigel et al.,[8] studying a subgroup of patients who had all obstructed vessels bypassed and patency of all grafts, could not produce angina in any and found that ischemic S-T changes in the electrocardiogram were abolished in 89 percent of patients. In contrast, the small group of patients with incomplete revascularization or graft failure, or both, showed no relief in angina pectoris or reduction in S-T segment change with exercise. Kouchoukos et al.,[9] studying a group of surgically treated patients with unstable angina, found marked improvement in the exercise ability of patients when all grafts were found to be patent, slight improvement when only one graft was patent and no improvement when all grafts were closed. The Cleveland Clinic[10] reported that 86.6 percent of patients who had complete revascularization had class I angina pectoris postoperatively compared with only 55.7 percent of patients who had incomplete revascularization.

Coronary bypass surgery not only relieves angina pectoris but also improves myocardial performance.[11] These effects had never been achieved with earlier forms of surgical treatment. The major mechanism responsible for the relief of angina pectoris and improved myocardial performance under stress has been demonstrated to be improved myocardial blood flow.[12] Other mechanisms of pain relief such as placebo effect

and interoperative infarction play a minor role. An increase in myocardial blood flow has been demonstrated with electromagnetic flowmeter measurements at surgery,[13] xenon washout studies[14] and, more recently, myocardial perfusion scanning techniques.[15]

The frequency with which patients obtain symptomatic relief and the duration of relief depends on several factors:

1. The relief of angina pectoris by coronary bypass surgery is determined by the degree of revascularization. This must be emphasized strongly because it is the most important factor in achieving the desired result. Obviously, it is desirable for all grafts to remain patent. Graft patency has increased with improved surgical experience. At Emory University Hospital 90 percent of grafts are patent 1 year after surgery. In a recent report from the Cleveland Clinic[16] there was little difference in graft patency rates between patients studied early and late; the patency rate was 82.6 percent in patients studied 48 months postoperatively. The Montreal Heart Institute[17] studied 98 patients 6 years postoperatively and found that the graft closure rate between year 1 and year 6 was only 10 percent. The factors that influence graft patency are the amount of arterial runoff, the size of the artery into which the graft is placed, the amount of graft flow and the experience of the surgeon. Unfortunately, not all symptomatic patients have suitable anatomy for coronary bypass surgery and many patients cannot benefit from surgery. At times, surgery is attempted on less than ideal vessels in an effort to help the patient. Obviously, some of the grafts to such arteries will not remain patent and all of the obstructed vessels may not be bypassed. In this group the greatest judgment and skill are needed to determine if grafting should be attempted.

2. Unfortunately, coronary atherosclerosis may continue to develop in the native vessels. As time passes, angina pectoris and other events, such as sudden death or infarction due to decreased coronary blood flow, may develop.

There is evidence that modern medical therapy for angina pectoris is superior to the medical treatment that was available 10 to 15 years ago. This improvement has been due to the use of propranolol, isosorbide dinitrate and nitroglycerin ointment. If this is true, it is proper to ask how often does modern medical therapy fail. Prospective randomized studies have shown that despite modern medical therapy that includes the use of propranolol, a significant number of patients will "cross over" from medical to surgical treatment. The number of "crossovers" was 17 percent in the Veterans Administration trial of patients with chronic angina pectoris[18] and 33 percent in the National Institutes of Health trial of patients with unstable angina pectoris.[7] When a significant number of patients in a randomized study cross over from the medical to surgical treatment, it is difficult or impossible to use the study to determine the longevity of patients originally assigned to the medical group. Fifty-four percent of the 17 percent who crossed over in the Veterans Administration study did so because of unacceptable angina pectoris.[18] In the National Institutes of Health study,[7] angina pectoris (classes III and IV) occurred during the follow-up period in 45 percent of the medically treated group and in 15 percent of the surgically treated group. Unacceptable angina pectoris led 33 percent of the medically treated patients to cross over to the surgical group in the National Institutes of Health trial.[7] *These data support the view that coronary bypass surgery is needed to relieve angina pectoris because it is virtually impossible to relieve angina pectoris in all patients with medical therapy even when propranolol and other modern drugs are used.* Unfortunately, too, not all patients can tolerate propranolol.

3. We must remember that patients with operable obstructive coronary disease who have angina pectoris may also have other types of chest discomfort. For example, some patients also have chest discomfort due to esophageal reflux and spasm, anxiety (neurocirculatory asthenia), chest wall pain, or other factors. One or more of these conditions may account for the continued chest discomfort in some patients after coronary bypass surgery.

Dangers of Procrastination

One can properly ask what harm can come by delaying surgery in patients who are "getting by" with their angina pectoris? Regrettably, sudden death, episodes of increasing angina pectoris and myocardial infarction may occur. Plotnick and Conti[19] performed coronary arteriography and left ventriculography in patients with unstable angina pectoris and separated them into two groups: patients who could be operated on but were *not* operated on (Group I) and patients whose condition was inoperable (Group II). The first year mortality rate in Group I was 9.5 percent. There were no additional deaths for 3 more years, but 14 percent of the patients had a nonfatal myocardial infarction and 50 percent had class III angina pectoris. One reason for the low mortality rate after the first year was that one third of their patients in Group I had single vessel obstruction. About 17 percent of the patients in this group were offered surgical treatment because medical management was not satisfactory. The first year mortality rate in Group II was 18 percent. After this initial mortality the incidence rate of nonfatal infarction was 27 percent, and 50 percent of the patients had class III angina. The mortality rate in 3 more years was 36 percent. All patients entered into the study had angina at rest that was of recent onset (12 patients) or had evolved from a pattern of stable angina on effort (20 patients). The first year mortality rate was unacceptably high in Group I, and the number of infarcts and the amount of angina that occurred after the first year indicate that the condition of many of the patients was becoming inoperable. *Could it be that delaying surgery in some patients with angina pectoris results in an inoperable status?*

One of us (J.W.H.) selected 24 patients with unstable angina pectoris that matched those described by Plotnick and Conti except that almost all of the patients had double or triple vessel obstruction (Fig. 1). There were no operative deaths in the group and no deaths in fol-

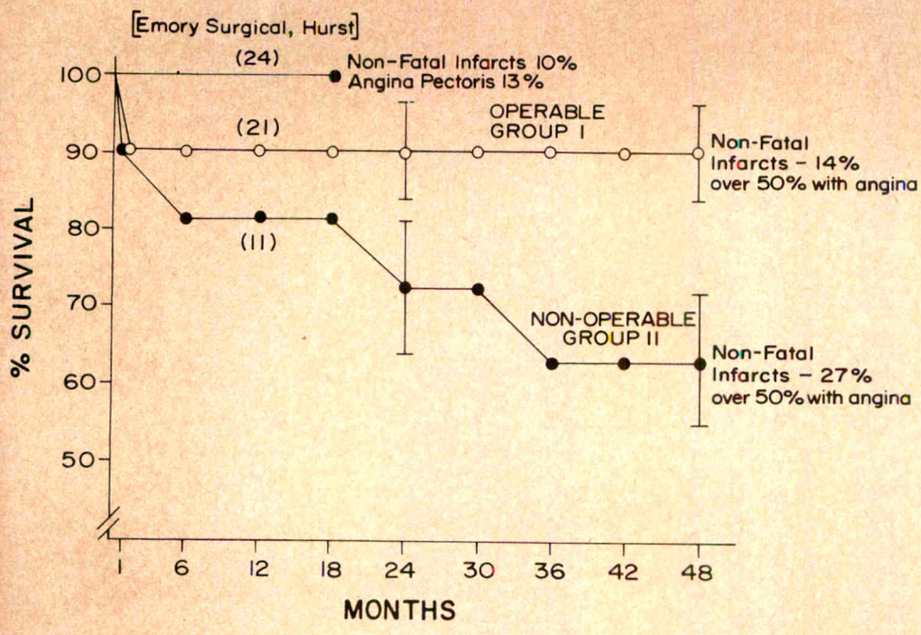

FIGURE 1. Survival curves and incidence of angina pectoris and nonfatal infarcts in two groups of medically treated patients reported on by Plotnick and Conti[19] and in a surgical group of patients at Emory University Hospital **(upper curve)** matched according to the symptoms described by Plotnick and Conti (see text). The medically treated patients in Group I **(middle curve)** had unstable angina pectoris and were classified as operable but were not operated on; those in Group II had unstable angina pectoris and were classified as inoperable. (The two lower curves are reprinted by permission of Plotnick and Conti[19] and *The American Journal of Medicine*.)

low-up at 1 to 2 years compared with the 9.5 percent first year mortality rate in their group. In the light of this experience, it is difficult for us to delay surgery when it is clear that many patients will die or enter an inoperable state if one waits and hopes that all will go well.

Prolongation of Life

Mortality due to coronary atherosclerotic heart disease is closely related to the degree of impairment of myocardial perfusion. This degree of impairment is determined by the number of obstructed arteries. *It should not surprise one that techniques that improve myocardial perfusion and relieve angina pectoris can also prolong life.* However, it is much more difficult to document improved survival than relief of angina pectoris. After all, a change in the symptomatic status of patients can be demonstrated with each patient acting as his own control. A change in longevity is much more difficult to measure because no one can say with assurance how long an individual patient will live. There is no way to study longevity in the individual patient, and the clinical trials performed to date are flawed. Nonetheless, because clinical decisions must be made, it is necessary to examine the results of the available studies and determine the direction of the evidence.

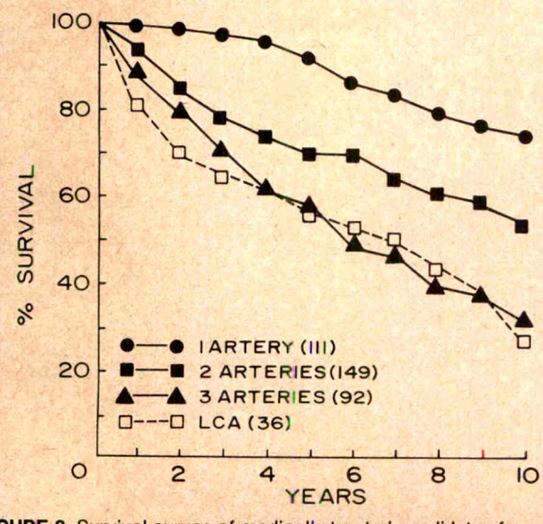

FIGURE 2. Survival curves of medically treated candidates for partial or complete revascularization (see text). LCA = left main coronary artery. (Reprinted by permission of Bruschke[24] and the Cleveland Clinic.)

Richards et al.[20] reported the 25 year follow-up results in 456 patients with angina pectoris. The annual mortality rate was 5 percent for the first 5 years and the cumulative mortality rate at 10 years was 41 percent. The annual mortality rate of patients with unstable angina pectoris is even higher.[19,21] However, with the development of coronary arteriography, it was discovered that some patients who were thought clinically to have coronary atherosclerotic heart disease in fact had normal coronary arteries. Accordingly, an answer to the question regarding prolongation of life requires that all patients in a study group have coronary arteriography and left ventriculography.

We will first make some general comments and present some cumulative data that compare the survival of patients treated medically with patients treated with bypass surgery. Specific subsets of patients will then be discussed. The most sensitive predictors of survival are the number of coronary arteries involved and the degree of left ventricular damage.[22] Accordingly, we will ex-

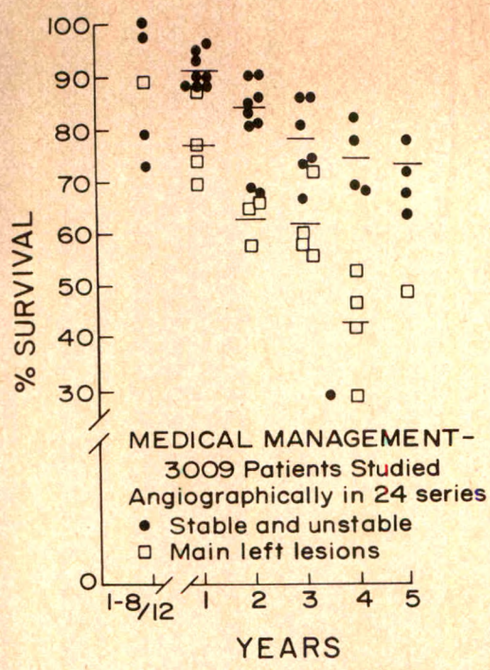

FIGURE 3. Compilation of the survival data of patients treated medically and reported in 24 different series of patients. We thank David Greene and his colleagues[25] for permitting us to reproduce the graph.

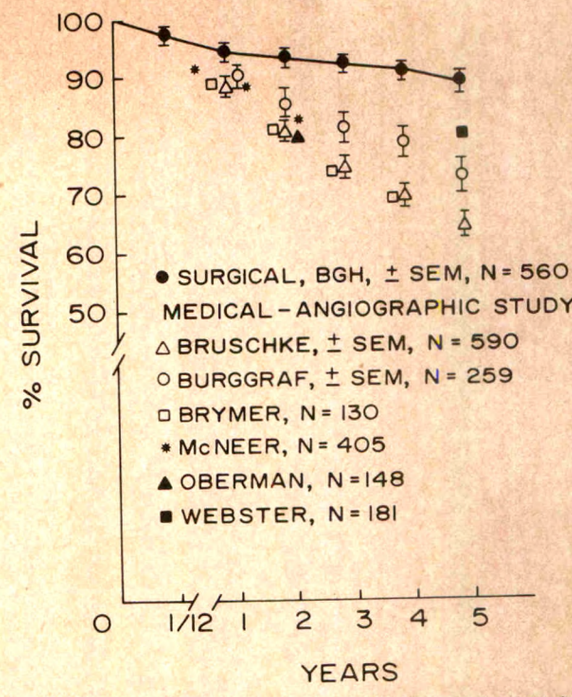

FIGURE 4. Survival curves of patients who had bypass surgery at the Buffalo General Hospital (BGH) and of six medically treated groups[26–31] (see text). N = number of patients; SEM = standard error of the mean. We thank David Greene and his colleagues[25] for permitting us to reproduce the graph.

amine and discuss separately patients with obstruction of the left main coronary artery, those with triple, double, and single vessel obstruction and those with normal and abnormal ventricular contractions.

General Comments and Cumulative Data

We are grateful to Mason Sones at the Cleveland Clinic for his development of coronary arteriography.[23] This procedure, with its modern modifications, has clarified many diagnostic problems and was the forerunner of modern bypass surgery. The persistence of Sones made it possible for the workers at the Cleveland Clinic to codify the patients who were sent to them during the mid 1960's and to follow up the patients, in concert with the referring physician, for 10 years. Many workers at the Cleveland Clinic, including Proudfit, Bruschke, Sheldon and others, participated in the follow-up studies of these patients.

Survival curves of medically versus surgically treated patients: Bruschke[24] reported the 10 year follow-up study of 601 patients at the Cleveland Clinic who were not operated on because bypass surgery was not yet available but who could have been operated on by modern criteria. The survival curves for patients with obstruction of the left main coronary artery and for patients with obstruction of three or two vessels and of one vessel are shown in Figure 2. It has been said that survival curves created during that time period represent the best data on the natural history of coronary atherosclerotic heart disease. The patients managed during that period received medical treatment such as advice regarding rest and activity, administration of nitroglycerin and administration of certain long-acting nitrates of questionable value. Propranolol, isosorbide dinitrate and nitroglycerin ointment have only been used properly and extensively during the current decade. The Cleveland Clinic curves (Fig. 2) are shown here for two reasons: (1) The reader can more readily perceive the seriousness of the disease in a display such as this, and (2) we will refer to these curves later when we compare the survival curves of more recently treated patients with the survival curves of patients treated during the earlier time period.

Greene and his colleagues[25] at the Buffalo General Hospital presented their elegant work in an exhibit at the Annual Meeting of the American Heart Association (December 1977).[25] Their chart (Fig. 3) shows the 5 year survival rate of 3,009 patients studied angiographically and treated medically in 24 reported series. They separated the patients into those with stable and unstable angina and those with obstruction of the left main coronary artery. The 5 year survival rates are similar to those observed in the curves of Bruschke[24] (Fig. 2).

Figure 4 compares the survival curve of all patients who were operated on at the Buffalo General Hospital[25] with that of six medically treated groups.[26–31] This retrospective matched study has the disadvantage of comparing more recent and vastly improved bypass surgery with older medical treatment when it is now thought that medical management has improved during the last few years. This criticism would require proof

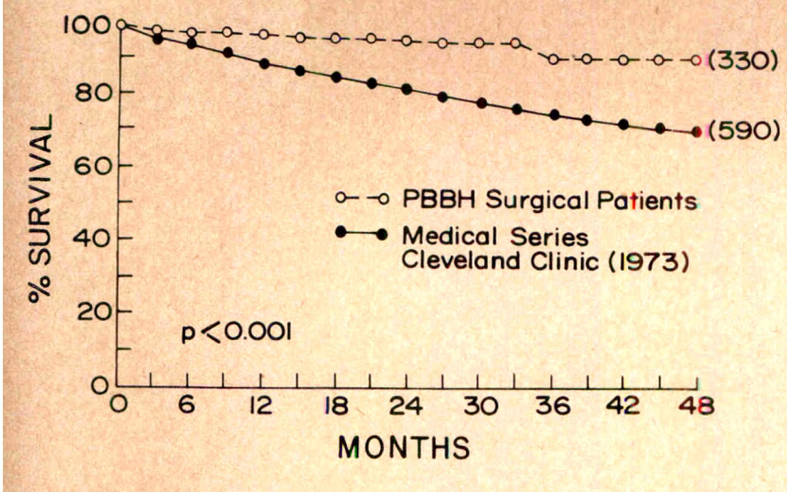

FIGURE 5. Survival curves of all patients operated on at the Peter Bent Brigham Hospital (PBBH) and of medically treated patients reported on by the Cleveland Clinic (1973). p = probability. (Reproduced with the permission of Cohn et al.[32] and *The American Journal of Surgery*.)

that more recent medical management is truly better than earlier medical management and that surgical treatment has reached its zenith. We mention the criticism to let the reader know that we are aware of the problem. However, we believe that such data cannot be discounted because all patients will not adhere to excellent medical management when it is prescribed over a 10 year period of time. Remember, some patients cannot tolerate propranolol. We use the comparison also to develop what appears to us to be a gestalt regarding the problem that is perceived only by recording the history of the development. Greene et al.[25] also presented data showing that many medical centers have achieved surgical results such as theirs.

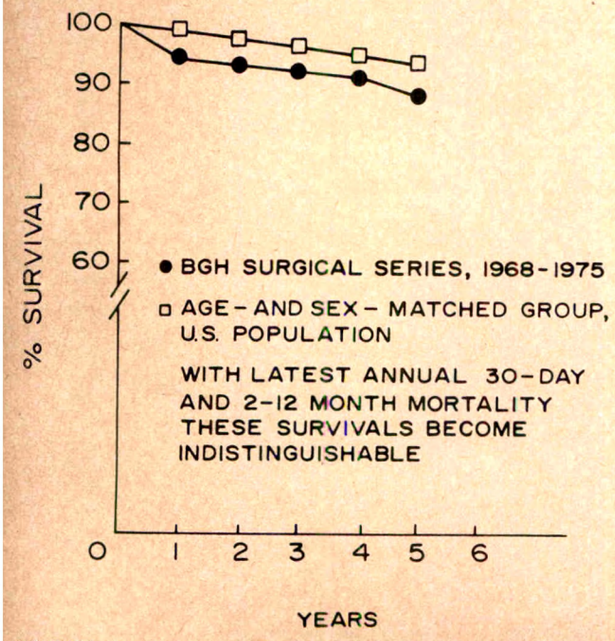

FIGURE 6. Survival curves of patients treated surgically at the Buffalo General Hospital (BGH) and of a group of patients, matched for age and sex, from the general population. We thank David Greene and his colleagues[25] for permitting us to reproduce this graph.

Cohn et al.[32] of the Peter Bent Brigham Hospital in Boston reported a cumulative survival rate of 95 percent at 48 months for all of their patients who had bypass surgery. The cumulative survival rate for the medically treated group reported by the Cleveland Clinic was 70 percent[34] (Fig. 5).

Survival curves of surgically treated patients compared with those of the general population: Greene et al.[25] compared the survival curve of all of their surgical patients with the survival curve of the general population of the United States (Fig. 6). The patients were matched according to age and sex. The cumulative survival rate at 5 years was about 90 percent in the surgical group and about 95 percent in the general population. These workers point out that, if their latest annual 30 day and 2 to 12 month mortality rates are used, the survival curve for surgically treated patients becomes indistinguishable from that of subjects from the general population. The Buffalo group have shown a remarkable phenomenon: Their 5 year cumulative survival rate for surgically treated patients differs by only 5 to 10 percentage points among patients with left main coronary arterial obstruction and those with triple, double or single vessel obstruction.

Spencer et al.[33] pointed out in 1974 that patients operated on at their institution had a 5 year cumulative survival curve of 81 percent. The expected survival in a group of persons from the general population of similar age, race and sex was 92 percent. The surgical technique has improved since then, and the United States life tables used by Spencer et al. were for 1965 and more recent life tables are now available.

Lawrie et al.[34] reported the following information regarding the long-term fate of 434 consecutive patients operated on between 1968 and 1971:

The average crude annual attrition rate after the first year was 2.3 percent per year, which approximates that of the general U.S. population after correction for age and sex. In the next 677 consecutive patients the survival rate after 5 years

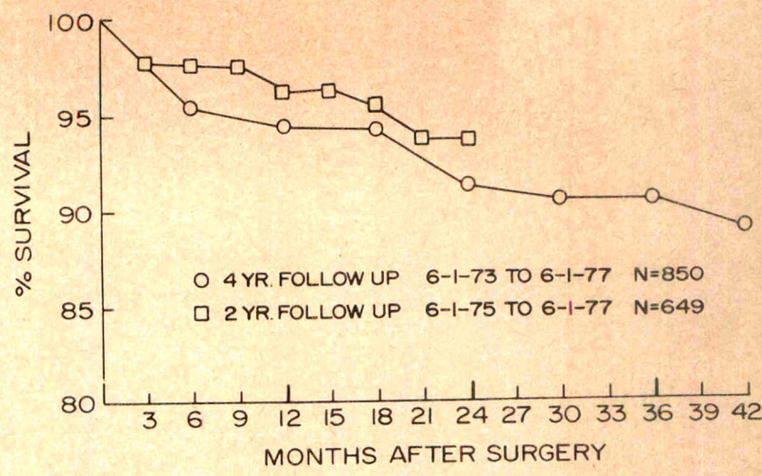

FIGURE 7. Survival curves of patients who had bypass surgery at Emory University Hospital. The **lower curve** shows the follow-up results in patients who entered the study between June 1, 1973 and June 1, 1977. The **upper curve** shows those of patients who entered the study during the last 2 years (from June 1, 1975 to June 1, 1977). N = number of patients.

was 91.4 percent (including 4.7 percent operative mortality rate) compared with the survival rate of a similar normal population of 92.7 percent. The operative mortality rate of 7.1 percent in this early experience has been reduced to less than 2 percent in current experience. These results suggest that the coronary bypass procedure provides sustained symptomatic relief and may prolong life.

Lawrie et al.[35] also reported the following in the *New England Journal of Medicine* as a rebuttal to Murphy's article[18] that appeared in the September issue of that Journal:

Recently, we have completed follow-up observation of 1108 consecutive surgical patients, 90 percent male with a mean age of 50.1 years, operated upon between 1971 and 1972 and all followed beyond five years. All patients were symptomatic, and double-vessel disease (>70 percent stenosis) was present in 413 patients (37.3 percent) and triple-vessel disease in 416 patients (37.6 percent). Left-main-coronary-artery disease was presented in 83 patients (7.5 percent). Left ventricular function was normal in only 36 percent of patients and was significantly impaired with an end-diastolic pressure over 15 mm Hg in 31 percent of patients (range, 15 to 55 mm Hg). Excluding left-main-coronary-artery disease, operative mortality overall was 3.5 percent. Overall survival (excluding left-main-coronary-artery disease) beyond five years was 90.0 percent (927/1025). Survival in patients with preoperative end-diastolic pressure below 15 mm Hg was 93.2 percent (695/746) overall. According to J. Brock, actuarial director of the Prudential Insurance Company, Houston, survival of a population of identical age and sex distribution not known to have heart disease was 92.7 percent. Thus, survival after coronary bypass in our experience approaches that of a normal population. The improved survival in our series, we believe, cannot be attributed to patient selection.

Austen[36] has given us permission to use the following statement prepared by him:

Just for the record, let me emphasize that our present hospital mortality for elective coronary artery surgery at the Massachusetts General Hospital is 1.5%. This includes some cases with ejection fractions of 20% or less. Our patency rate at the end of a year is approximately 90%. Our five-year survival is similar to the reports from other institutions—88% survival at five years—about the same survival as would be expected in the age, race and sex matched group of individuals in the general population.

Kirklin[37] has given us permission to use the new data that he and his colleagues have collected at the University of Alabama. They compared the survival curves of medically treated patients reported on by the Veterans Administration with their surgical group and the survival curves of persons from the general population (matched for age, race and sex). They studied patients with left main coronary obstruction and triple, double or single vessel obstruction. The results, which are truly remarkable, will be described later.

The cumulative survival curve of patients who had bypass surgery at Emory University Hospital is shown in Figure 7. The 42 month cumulative survival rate for the 850 patients operated on between June 1, 1973 and June 1, 1977 was 90 percent and the 24 month cumula-

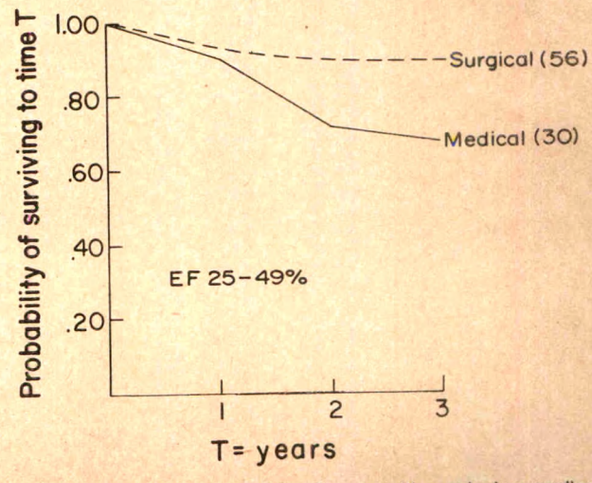

FIGURE 8. Probability of surviving 3 years with surgical or medical treatment in patients with an ejection fraction (EF) of 25 to 49 percent. (Reproduced with permission of Vlietstra et al.[38] and the *Mayo Clinic Proceedings*.)

tive survival rate for the 649 patients operated on between June 1, 1975 and June 1, 1977 was 94 percent. These curves are shown to point out that our own experience with bypass surgery is similar to that of Greene, Kirklin, Lawrie, Austen and others who are now achieving a 4 to 5 year cumulative survival rate of 90 to 95 percent.

It is beginning to appear that when a skilled surgical team operates on the appropriate patients they can achieve a 1 percent hospital mortality rate, complete revascularization, a graft patency rate of 90 percent and a 4 to 6 percent perioperative infarction rate. Under such circumstances, it is possible to promise a 90 to 95 percent 5 year cumulative survival rate.

Prognostic role of ejection fraction: Many studies have shown that the level of the ejection fraction profoundly influences the survival of patients with coronary atherosclerotic heart disease. Vlietstra and his colleagues[38] at the Mayo Clinic studied this problem extensively using a prospective matched method. They found that among patients with an ejection fraction of 25 to 49 percent the survival of those receiving bypass surgery was much better than that of patients receiving medical management (Fig. 8). It seems that one can observe a difference in survival between medically and surgically treated groups within 3 years by choosing patients who have an abnormal ejection fraction. It also seems likely that survival differences between the two groups may not be evident until after 3 or 4 years in patients who have a normal ejection fraction.

Incidence of sudden death: Patients with coronary atherosclerotic heart disease are made ill by angina pectoris, myocardial infarction, heart failure including a profound fatigue on effort, shock and arrhythmias. Patients with coronary atherosclerotic heart disease die as a result of sudden death, usually from a cardiac arrhythmia but occasionally from acute electrical mechanical dissociation, chronic heart failure or myocardial infarction with acute heart failure, arrhythmia or shock. Because sudden death occurs in about 50 percent of those who die of coronary atherosclerotic heart disease it seems proper to present data to support the view that coronary bypass surgery is more reliable than medical management in preventing sudden death.

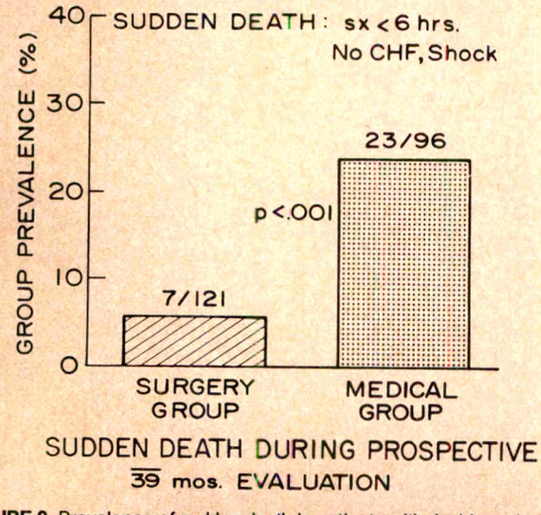

FIGURE 9. Prevalence of sudden death in patients with double and triple vessel obstruction. CHF = congestive heart failure; p = probability; sx = symptoms. (We thank Vismara et al.[40] for permission to reproduce this graph.)

Hammermeister et al.[39] reported on sudden deaths in medically and surgically treated patients. Their study was prospective and their patients were angiographically matched. The follow-up period was 4 years. They studied the effect of three different categories of ejection fraction in patients with one, two and three vessel obstruction. The percent of patients who died suddenly was less in every category of surgically treated patients than in the matched medical group. The authors state[38]:

> The sudden death rates for subgroups of medically treated patients were 1.8 to 10.9 times higher than the rates in subgroups of surgically treated patients with a comparable extent of coronary disease and ejection fraction.

Vismara et al.[40] found that the prevalence rate of sudden death in surgically treated patients with double or triple vessel obstruction was about one third that in the medically treated group (Fig. 9).[39] Their study was prospective using angiographically matched patients, and the follow-up period was 39 months.

The Hines Veterans Administration Hospital participated in the Veterans Administration randomized study of angiographically matched patients with chronic stable angina pectoris.[41] The Hines group contributed 20 percent of the patients in the total cooperative study. At 5 years the cumulative survival rate was about 90 percent for the Hines surgical group compared with 70 percent in the Hines medical group.

Angina pectoris: Cohn et al.[32] also reported the results of bypass surgery in patients with "preinfarction" angina pectoris. Their study was retrospective, and the medical group with which the surgical patients were compared was the group reported on by Gazes et al.[21] (Fig. 10). The first year cumulative survival rate was about 80 percent in that medical group and about 98 percent in the surgical group. The 4 year cumulative survival rate was about 70 percent in the medical group and about 95 percent in the surgical group.

The study by Cohn et al.[32] shows a remarkable survival rate in the surgical group of patients with "preinfarction" angina. We know of no medical group with such a good survival rate. The study is criticized, however, because it compares modern surgery with medical treatment given during an earlier time period. Then too, Gazes et al.[21] studied their patients without the benefit of angiography. We recommend that the reader look carefully at the report of Plotnick and Conti.[19] We discussed the report in detail earlier in the section on "Dangers of Procrastination." Plotnick and Conti[19] have shown us once again that unstable angina pectoris is a very dangerous condition. Furthermore, it is dangerous even with modern medical management. They

observed a first year mortality rate of 9.5 percent in the group that could have had bypass surgery but did not and a 1 year mortality rate of 18 percent in patients whose condition was not operable. One of us (J.W.H.) carefully matched the clinical histories of 24 patients operated on at Emory University Hospital during 1976 with those of the patients reported on by Plotnick and Conti (Fig. 1). There was no operative mortality in the Emory group, and all patients were alive in April 1978. The majority of patients operated on at Emory have unstable angina pectoris. The operative mortality rate is about 1 percent and the cumulative survival rate at 42 months is about 90 percent. Because of these results, we could not randomize our patients with unstable angina pectoris.

The National Institutes of Health study of angina

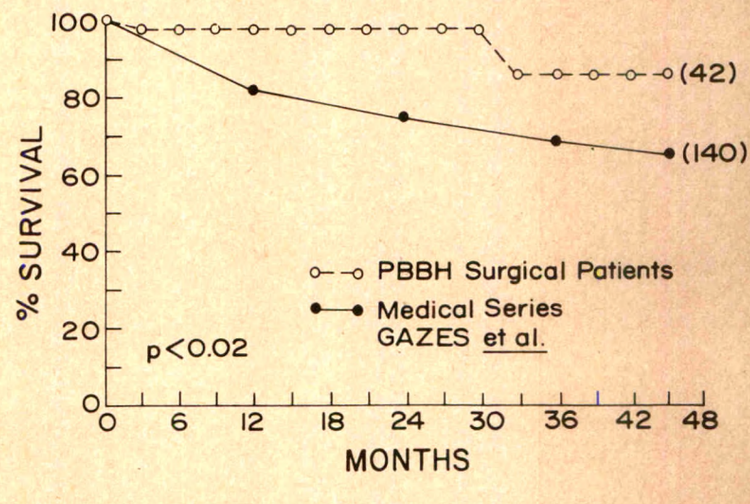

FIGURE 10. Cumulative survival rates at 48 months of patients with "preinfarction angina" operated on at the Peter Bent Brigham Hospital (PBBH) and of patients treated medically and reported on by Gazes et al.[21] p = probability. (Reproduced with permission of Cohn et al.[32] and *The American Journal of Surgery*.)

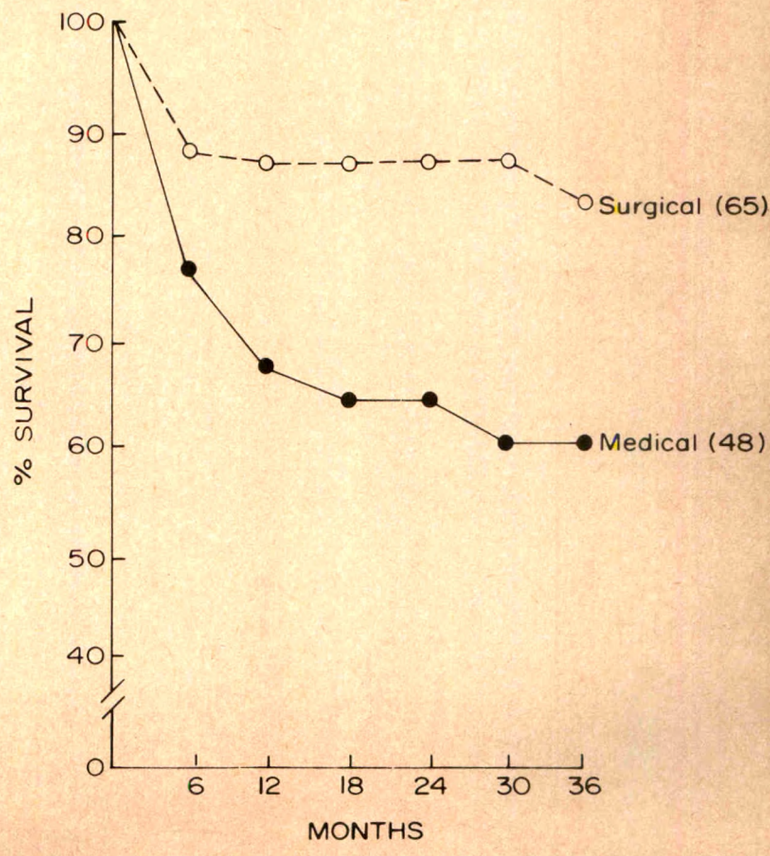

FIGURE 11. Results of the Veterans Administration prospective randomized clinical trial of patients with obstruction of the left main coronary artery. (Reproduced from *Circulation* with permission of Takaro et al.[42] and the American Heart Association, Inc.)

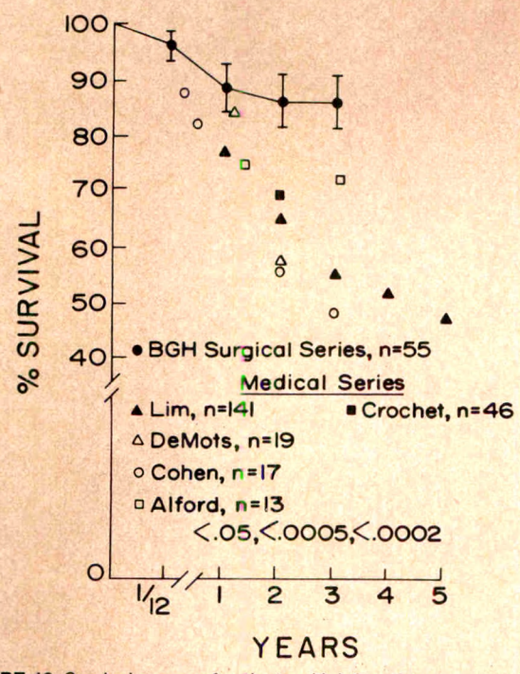

FIGURE 12. Survival curves of patients with left main coronary arterial obstruction treated with bypass surgery at Buffalo General Hospital (BGH) and treated medically as reported on by Lim,[43] DeMots,[44] Cohen,[45] Alford[46] and Crochet[47] and their co-workers. n = number of patients. (Reproduced with permission of Greene et al.[25])

pectoris[7] was not designed to study long-term survival but to determine how urgent it is to operate immediately on patients with unstable angina pectoris. Because 33 percent of the patients studied "crossed over" from the medical to the surgical group as a result of unacceptable angina pectoris, this particular study cannot be used to determine the survival curve of patients with unstable angina. This clinical trial was a randomized prospective study, but it is very difficult to achieve perfect randomization once it is known that one method of treatment is failing (medical treatment would soon be known as failing when 33 percent could not be retained in the medical group because of unacceptable angina pectoris). It is also difficult to define the pool of patients from which the patients in the study were selected for randomization because the pool of patients with unstable angina in the institutions was much larger than the small study group.

It appears to us that retrospective matched studies, prospective matched studies, prospective randomized studies and comparison of results in surgically treated patients to the life table data all support the view that modern bypass surgery relieves angina pectoris and prolongs life in properly selected patients. We will later show that when specific subsets of patients are identified it is possible to prove with even greater assurance that, in comparison with modern medical management, modern coronary bypass surgery prolongs life.

Left Main Coronary Arterial Obstruction

The patients with left main coronary arterial obstruction treated medically and reported on by the Cleveland Clinic[24] had a 5 year cumulative survival rate of less than 57 percent and a 10 year cumulative survival rate of 25 percent (Fig. 2).

The patients with left main coronary arterial obstruction treated medically in the Veterans Administration prospective randomized study[42] had a cumulative survival rate of about 68 percent at 1 year and 61 percent in 3 years (Fig. 11). The cumulative survival rate of the surgically treated group was 88 percent at 1 year and 83 percent at 3 years. The difference in the cumulative survival rate between the surgical and medical groups was even more striking when patients with abnormal left ventricular function were considered. This particular clinical trial was so conclusive that neither the Veterans Administration nor anyone else will ever again randomize patients with left main coronary arterial obstruction. Other retrospective medical series have shown similar findings. Greene et al.[25] compared the results in surgically treated patients with left main coronary arterial obstruction with those in five series of medically treated patients.[43–47] The results, which favor bypass surgery, are shown in Figure 12.

Figure 13 shows the superimposed cumulative survival curves of the Veterans Administration medically treated group[42] (follow-up period 3 years) and those of the medically treated (follow-up period 10 years) and surgically treated (follow-up period 6 years) patients reported on by the Cleveland Clinic.[48] The 6 year cumulative survival rate for patients at the Cleveland Clinic was about 88 percent for those treated with bypass surgery and about 52 percent for those treated medically. The 3 year cumulative survival rate was about 90 percent for the group treated with bypass surgery at the Cleveland Clinic compared with about 61 percent for the Veterans Administration medical group. Medical management fared less well in the Veterans Administration study than in the Cleveland Clinic study, although the former was performed during a later time period than the latter.

Kirklin[37] compared the survival curve of surgically treated patients at the University of Alabama who had left main coronary arterial obstruction with the survival curve of a group of persons from the general population who were matched for age, sex and race. The survival curve for the latter group was constructed from data from the 1974 U.S. life tables generated by the Department of Health, Education, and Welfare. He also compared the survival curve of the Veterans Administration medically treated group with the survival curve of persons from the general population of similar age, sex and race. The survival curve for the latter group was also constructed from data from the 1974 U.S. life tables. The 5 year cumulative survival rate was about 96 percent for the members of the general population matched with the Veterans Administration medical group and about 63 percent for patients in the latter group with left main coronary arterial obstruction. The 5 year cumulative survival rate was about 94 percent for the members of the general population matched with Kirklin's surgical group and about 87 percent in the latter group. These data show the long-term results of

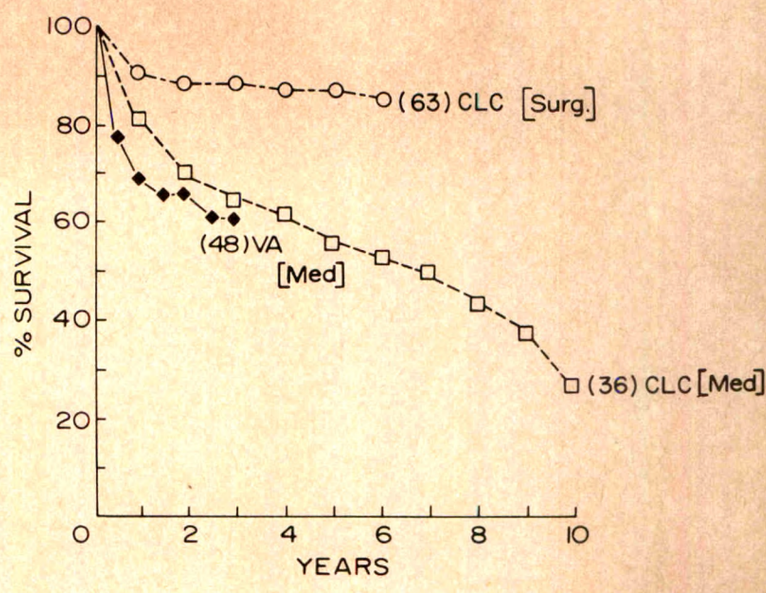

FIGURE 13. Survival curve of patients with obstruction of the left main coronary artery treated with coronary bypass surgery (Surg.) at the Cleveland Clinic (CLC) (**upper curve**) and treated medically (Med.) at the Cleveland Clinic (**middle curve**) or by the Veterans Administration (VA) groups (**lower curve**).[42]

the hospital survivors after coronary artery bypass grafting; the data are only slightly altered if a group of workers reports a 1 percent hospital mortality rate.

In Figure 14 the survival curve of the patients at Emory University Hospital with left main coronary arterial obstruction who had coronary bypass surgery is superimposed on that of the Veterans Administration medically treated patients.[42] Since 1973, our surgical team has operated on and we have followed up 124 patients with left main coronary obstruction. The cumulative survival rate of this group was 86 percent at 3 years compared with the 61 percent cumulative survival rate of the Veterans Administration medical group.[42] With the improved surgical techniques of the past 2 years, 88 patients have been operated on at Emory University Hospital; the 18 month cumulative survival rate is about 94 percent in this group but only about 65 percent in the medical group reported on by the Veterans Administration.

From time to time an article appears proclaiming that patients with left main coronary obstruction may live a long time.[49] Sometimes the reports imply that the condition may not be dangerous. Figure 2 shows clearly that there is a pool of patients with left main coronary arterial obstruction who have had the condition for 10 years. (Note that the cumulative survival rate is 25 percent at 10 years.) Accordingly, a physician may encounter such patients. Those patients are fortunate because the chances are overwhelming that they will not live 10 years with this condition. In fact, there is a 50 percent chance that such a patient will not live 5 years and a 20 percent chance that the patient will be dead in 1 year (Fig. 2). The issue is not whether there are patients who survive 10 years with left main coronary arterial obstruction, but what chance they have to do so.

Triple Vessel Obstruction

When survival curves of medically treated patients with triple vessel coronary obstruction are analyzed,

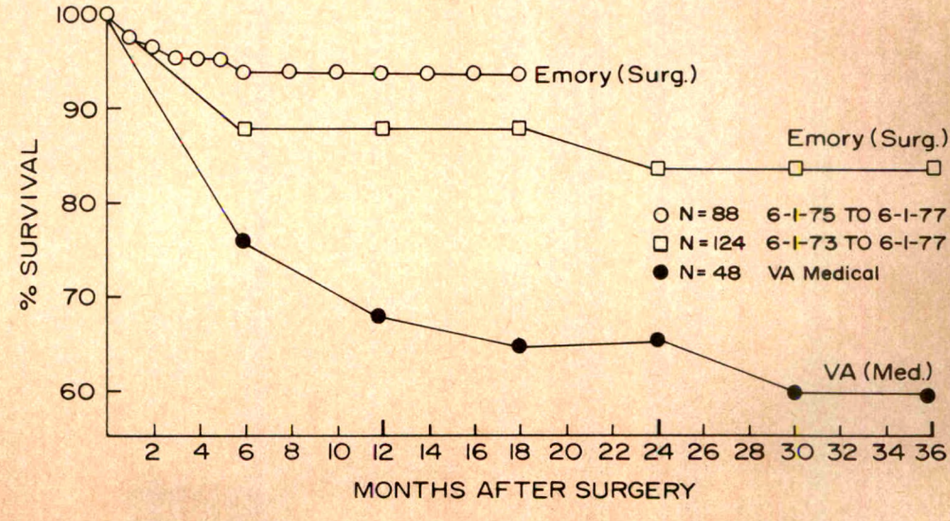

FIGURE 14. Survival curves of patients with obstruction of the left main coronary artery treated medically (Med.) by the Veterans Administration (VA) groups (**lower curve**) and with bypass surgery (Surg.) at Emory University Hospital between June 1, 1973 and June 1, 1977 (**middle curve**) and between June 1, 1975 and June 1, 1977 (**upper curve**). N = number of patients.

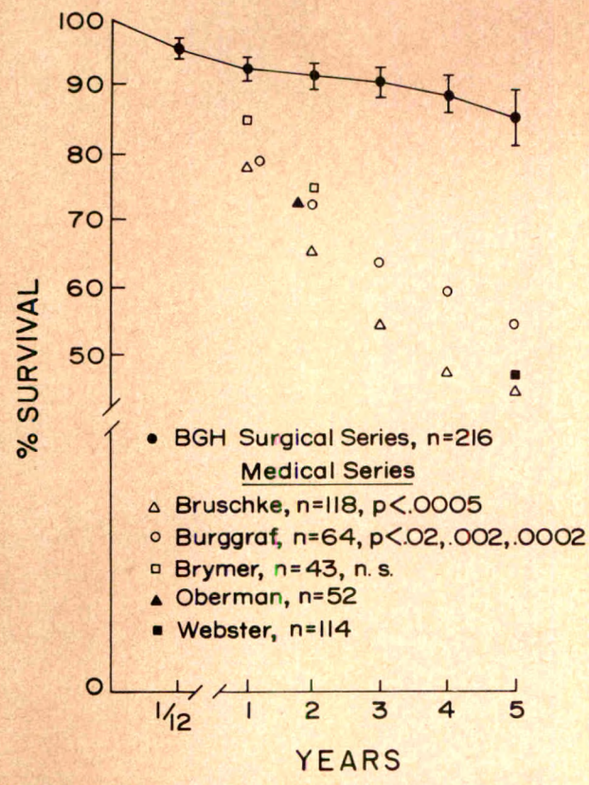

FIGURE 15. Survival curves of patients with triple vessel obstruction treated with bypass surgery at the Buffalo General Hospital (BGH) and treated medically in five series.[26–31] n = number of patients; n.s. = not significant; p = probability. (Reproduced with permission of Greene et al.[25])

they differ very little from the survival curves of medically treated patients with left main coronary arterial obstruction. The medically treated patients reported on by the Cleveland Clinic had a 56 percent cumulative survival rate at 5 years after patients in inoperable condition were excluded from analysis (Fig. 2). Parker[50] reported on the effect of abnormal left ventricular function on the survival of patients with triple vessel obstruction treated without surgery. Those with normal left ventricular contractility had a 5 year cumulative survival rate of 66 percent compared with a 40 percent rate for patients with normal left ventricular contractility.

Figure 15 depicts the 5 year survival curve of patients who had coronary bypass surgery at the Buffalo General Hospital.[25] The survival curve for surgically treated patients can be compared with the survival curves of five series of medically treated patients.[26–28,30,31] The cumulative survival rate is about 88 percent at 5 years in the surgically treated group compared with 48 to 58 percent in the medically treated patients. Cohn et al.,[41] working at the Peter Bent Brigham Hospital, reported a cumulative survival rate of 97 percent at 5 years in patients who had bypass surgery for triple vessel obstruction (Fig. 16). This compares with a 56 percent cumulative survival rate at 4 years in the medically treated patients reported on by the Cleveland Clinic.

The preceding studies compare the results of modern surgical management with the results of earlier medical management. However, it should be obvious that medical management would have to improve considerably to compare favorably with the results of surgery.

Kouchoukos et al.[9] recently reported the results of their patients who were operated on and followed up at the University of Alabama in Birmingham. The patients were not randomized, but the study was performed at one institution and the surgically treated and medically treated groups were observed and treated during the same time period. Figure 17 shows the survival curves for a group of patients who had coronary bypass surgery, a group who were surgical candidates but were not operated on and a group who had triple vessel obstruction but whose condition was inoperable. The cumulative survival rate at 46 months was 83 percent for the surgical group, 53 percent for the patients who could have been operated on but were not (medical treatment group) and 44 percent for the patients who could not be operated on. The medically treated patients whose condition was considered operable but who were not operated on undoubtedly received good medical treatment, but they did not fare nearly as well as the surgically treated group. Hammermeister et al.[39] reported

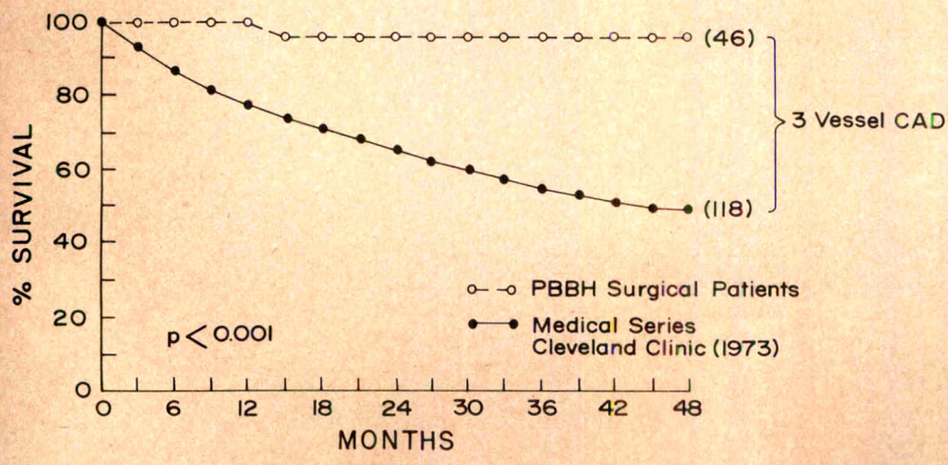

FIGURE 16. Survival curves of patients with triple vessel coronary artery disease (CAD) treated with bypass surgery at the Peter Bent Brigham Hospital (PBBH) and treated medically at the Cleveland Clinic (**lower curve**). p = probability. (Reproduced with permission of Cohn et al.[32] and *The American Journal of Surgery*.)

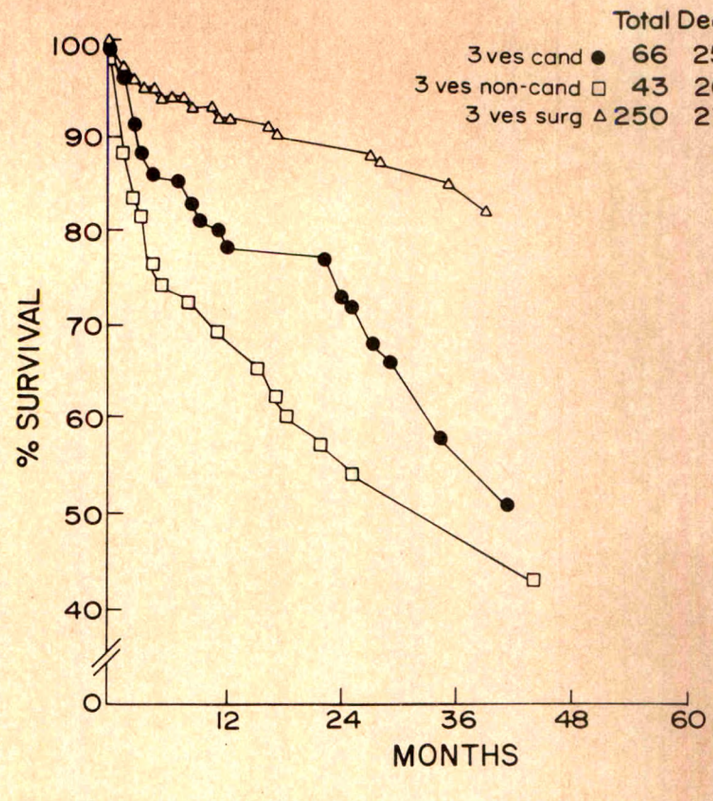

FIGURE 17. Survival curves of patients with triple vessel obstruction who were treated and followed up at the University of Alabama. The **upper curve** shows the survival curve of the patients who had bypass surgery (surg). The **middle curve** shows the survival curve of the patients who could have been operated on but were not (3 ves cand). The **lower curve** shows the survival curve for the patients who could not be operated on (non-cand). (Reproduced with the permission of Kouchoukos et al.[9] and F.A. Davis Company.)

the results in a prospective matched group of patients who were studied in the Seattle area. They found that, in comparison with medical treatment, bypass surgery improved survival in patients with an ejection fraction of 20 to 50 percent.

The first article[18] reporting the results of the Veterans Administration randomized study of patients with chronic stable angina pectoris appeared in September 1977. The report revealed the data on patients who were followed up for 3 years. Read et al.[51] reported the data on the same patients at 54 months in January 1978. The subset of patients with triple vessel obstruction and a mild to moderate decrease in left ventricular contractility deserves close scrutiny. There was little difference in the survival curves of the patients treated surgically and those treated medically when the patient follow-up period was only 3 years (Fig. 18). However, despite a high operative mortality rate, incomplete revascularization, poor graft patency and some "cross over" from the medical to the surgical group, the cumulative survival rate at 54 months was 85 percent for the surgical group compared with 76 percent for the medical group. In other words, the Veterans Administration study shows the benefit of surgical compared with medical treatment when the patient follow-up period is longer than 3 years. The learning curve in surgical treatment is of great importance. Unfortunately, the operative mortality during the early part of the Veterans Ad-

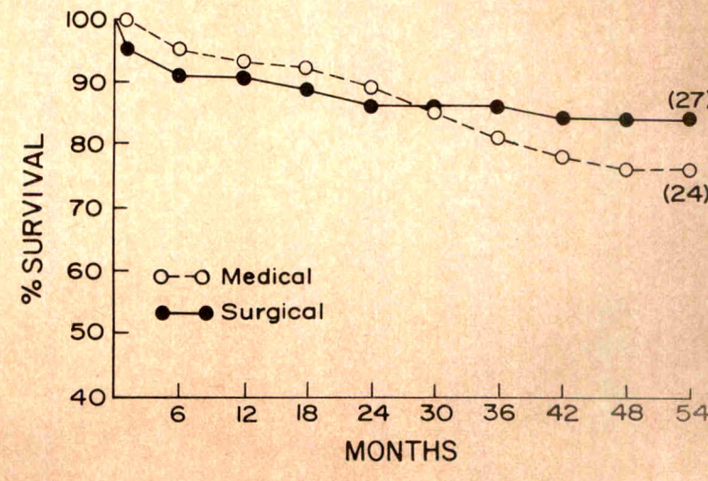

FIGURE 18. Survival curves of 129 medically and 105 surgically treated patients with triple vessel obstruction who had an abnormal left ventricle (from the Veterans Administration prospective randomized study of patients with chronic stable angina pectoris). (Reproduced with permission of Read et al.[51] and the *Journal of Thoracic and Cardiovascular Surgery*.)

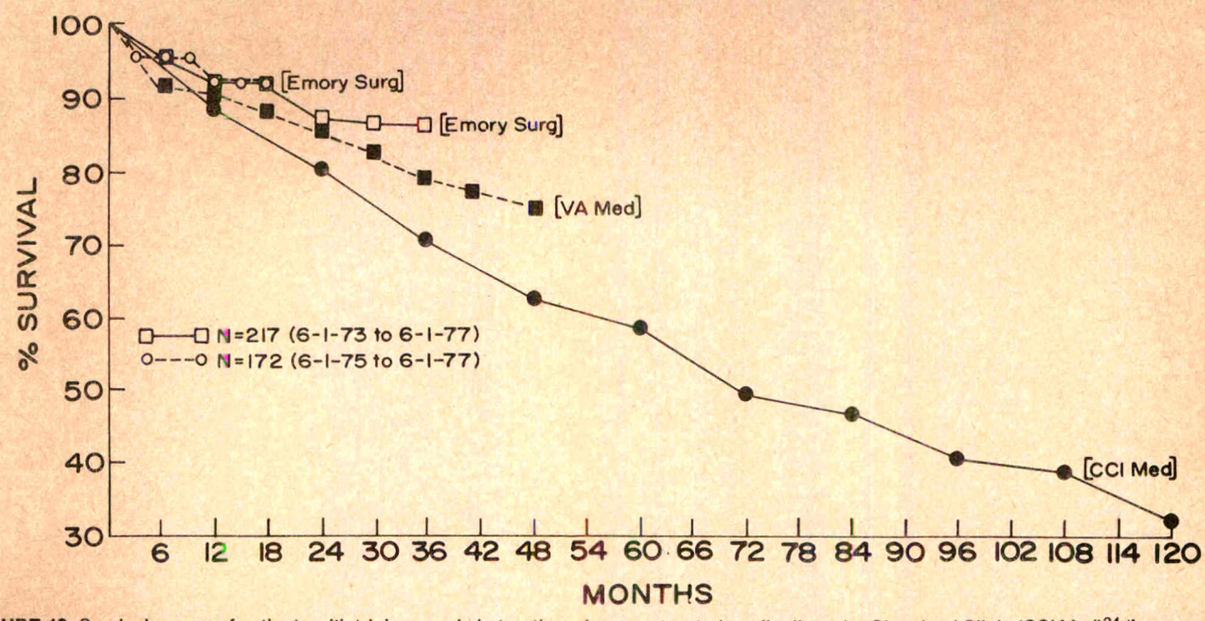

FIGURE 19. Survival curves of patients with triple vessel obstruction who were treated medically at the Cleveland Clinic (CCI Med)[24] **(lower curve)** and by the Veterans Administration group[51] (VA Med) **(black squares)** and treated with coronary bypass surgery (Surg) at Emory University Hospital from June 1, 1973 to June 1, 1977) **(open squares)** and from June 1, 1975 to June 1, 1977 **(open circles)**. N = number of patients.

ministration study was much greater, as it was in many centers, than it is today. Accordingly, we do not believe that the results of that study are relevant to the work done at centers where the operative risk is 1 percent.

McNeer et al.,[29] in a nonrandomized but matched study, found a subgroup of patients with triple vessel obstruction, abnormal left ventricular contraction and normal cardiac output. The cumulative survival rate was 94 percent at 24 months in the group operated on and 75 percent in those not operated on.

Kirklin[37] compared the survival curve of the Veterans Administration medically treated group of patients with triple vessel obstruction with the survival curve of persons from the general population who were matched for age, race and sex, constructed from data available in the 1974 U.S. life tables. The Veterans Administration medical group had a cumulative survival rate of about 74 percent, whereas that of persons from the general population was 95 percent at 5 years. The 5 year cumulative survival rate was about 89 percent for the group of patients treated surgically at the University of Alabama compared with 95 percent for the general population. These data show the long-term results of the hospital survivors after coronary bypass grafting. Again, the long-term results are only slightly altered if a group reports a 1 percent hospital mortality rate.

Figure 19 shows the superimposition of the survival curves of medically treated patients reported on by the Cleveland Clinic,[24] medically treated patients reported on in the Veterans Administration study of randomized patients with chronic stable angina pectoris,[51] patients in the Emory University Hospital 3 year follow-up study of patients who had coronary bypass surgery, and patients included in the Emory University Hospital results for the last 2 years of that study. It is highly likely that some patients treated medically and reported on by the Cleveland Clinic had unstable angina pectoris and others had stable angina pectoris. The majority of patients operated on at Emory University Hospital had unstable angina pectoris. The patients in the Veterans Administration clinical trial had chronic stable angina pectoris, and the majority had a normal left ventricle. We have therefore compared the Veterans Administration group, which was expected to have a good prognosis and has been said to have had excellent medical treatment, with the group treated medically at an earlier time and reported on by the Cleveland Clinic and with the sicker patients who had coronary bypass surgery at Emory University Hospital. In this way we believe we are giving every advantage to the Veterans Administration medical group and every disadvantage to our own surgical group. The cumulative survival rate at 36 months was 70 percent in the medical group reported on by the Cleveland Clinic and 80 percent in the medical group of patients with chronic stable angina pectoris reported on by the Veterans Administration. Thus there was a 10 percent difference in the 36 month cumulative survival rate of the Veterans Administration patients who were treated medically and those managed medically at the Cleveland Clinic. If one assumes that the entire difference is due to improved medical management, one is disappointed that there is only a 10 percent difference. Follow-up to 48 months shows that the difference is only about 14 percent. For the Emory surgical group the cumulative survival rate at 36 months was 88 percent and, with the improved surgical tech-

niques of the past two years, the cumulative survival rate at 18 months is 93 percent.

Double Vessel Obstruction

Medically treated patients with 75 percent cross-sectional stenosis of two major vessels have a better survival rate than those with three vessel obstruction. If the left anterior descending artery is one of the involved vessels, then survival may be less than when this vessel is not affected. The medically treated patients reported on by the Cleveland Clinic[24] had a 69 percent cumulative survival rate at 5 years after patients classified inoperable were excluded from the analysis (Fig. 2). Lichtlin[52] found a cumulative survival rate of 70 percent with a wide range based on the condition of the left ventricle.

Figure 20 depicts the 5 year survival curve for patients who received bypass surgery at Buffalo General Hospital.[25] The survival curve for surgically treated patients can be compared with the survival curves of five series of medically treated patients.[26–28,30,31] The cumulative survival rate for the surgical group was about 90 percent at 5 years compared with 63 to 65 percent in the medical groups. Cohn et al.[32] achieved a cumulative survival rate of 96 percent at 4 years in patients who had bypass surgery for double vessel obstruction (Fig. 21). This compares with a 72 percent cumulative survival rate at 4 years in the medically treated patients reported on by the Cleveland Clinic. The preceding studies compare the results of modern surgical management with the results of earlier medical management. Again, it should be obvious that medical management would have to improve considerably to compare favorably with surgical treatment.

Kouchoukos et al.[9] recently reported the results of their patients who were operated on and followed up at the University of Alabama in Birmingham. Again, the patients were not randomized, but the study was performed at the same institution, and the surgically treated and medically treated groups were observed and

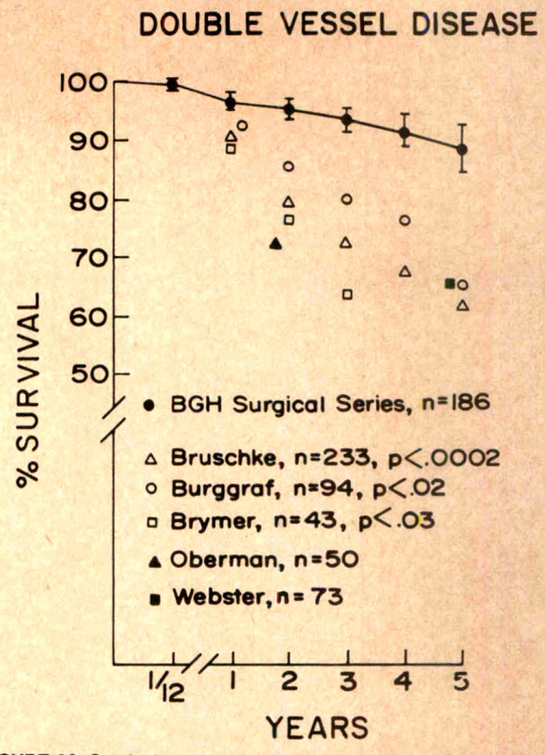

FIGURE 20. Survival curves of patients with double vessel obstruction treated with bypass surgery at the Buffalo General Hospital (BGH) (**upper curve**) and treated medically in five series.[26–31] n = number of patients; p = probability. (Reproduced with permission of Greene et al.[25])

treated during the same time period. Figure 22 shows the cumulative survival curves for a group of patients who had coronary bypass surgery, a group of patients who were surgical candidates but were not operated on and a group of patients who had double vessel obstruction but who were classified as inoperable. The respective cumulative survival rates at 24 months were 93, 84 and 73 percent. The medically treated patients

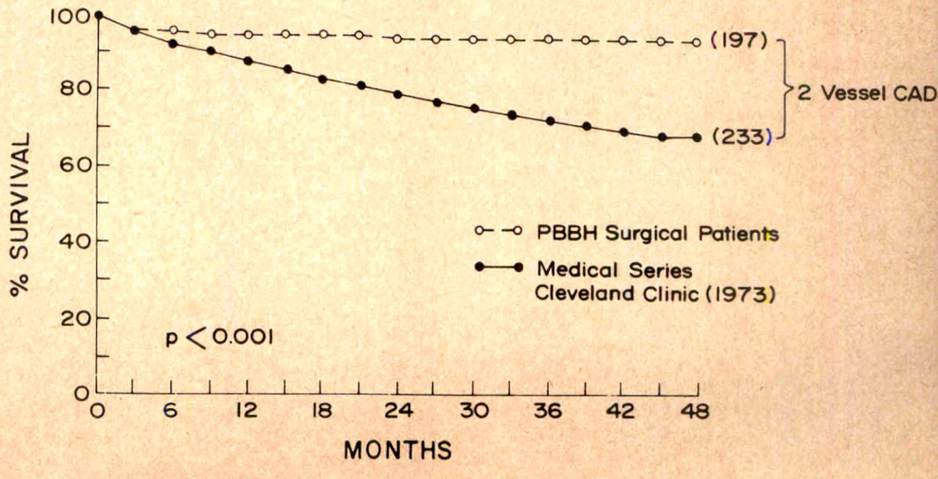

FIGURE 21. Survival curves of patients with double vessel coronary artery disease (CAD) treated with bypass surgery at the Peter Bent Brigham Hospital (PBBH) (**upper curve**) and treated medically at the Cleveland Clinic.[32] Figures in parentheses indicate number of patients; p = probability. (Reproduced with permission of Cohn et al.[32] and *The American Journal of Surgery.*)

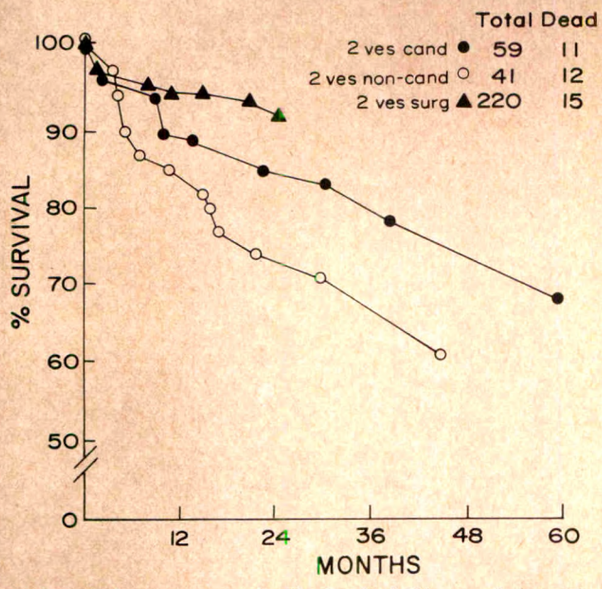

FIGURE 22. Survival curves of patients with double vessel obstruction who were treated and followed up at the University of Alabama. **Upper curve,** patients who had bypass surgery (surg); **middle curve,** patients who could have been operated on but were not (2 ves cand); **lower curve,** patients who could not be operated on (2 ves non-cand). (Reproduced with permission of Kouchoukos et al.[9] and F.A. Davis Company.)

classified as operable but not operated on undoubtedly received good medical treatment and did not fare nearly as well as the surgically treated group.

Hammermeister et al.[39] reported the results of medically and surgically treated patients in the Seattle Heart Watch. The study was a prospective one and the patients were matched according to 40 variables. Ninety-seven matched pairs were found. The cumulative survival rate was much better for the surgically treated than for the medically treated patients. When the ejection fraction was 31 to 50 percent of normal, the patients who had coronary bypass surgery fared much better than the patients with a similar ejection fraction who were treated medically.

Kirklin[37] compared the survival curve for the Veterans Administration medically treated patients with double vessel obstruction with that of persons from the general population who were matched for age, race and sex. Such a curve can be constructed by using data from the 1974 U.S. life tables. The respective survival rates were 87 and 94 percent. In comparison, Kirklin's group of patients treated surgically had a cumulative 5 year survival rate of 93 percent.

Figure 23 shows the superimposition of the cumulative survival curves of medically treated patients reported on by the Cleveland Clinic, medically treated patients reported on in the Veterans Administration study of randomized patients with chronic stable angina pectoris, patients in the Emory University Hospital 3 year follow-up study of patients who had coronary bypass surgery and patients in the last 2 years of that study. It must be remembered that the patients in the Veterans Administration medical group were all classified as operable and had chronic stable angina pectoris, and some patients crossed over to surgical therapy because of unacceptable angina pectoris; in contrast, the Emory University Hospital surgical group included many patients with an ejection fraction reduced to 20 percent and a large proportion of patients with unstable angina pectoris. Again, we have given every disadvantage to our own surgical group. The medically treated patients reported on by the Cleveland Clinic were treated at an earlier time period than the patients in the Veterans Administration study. The cumulative survival rate at 36 months was 82 percent in the Cleveland Clinic study and 88 percent in the patients with chronic stable angina pectoris in the Veterans Administration

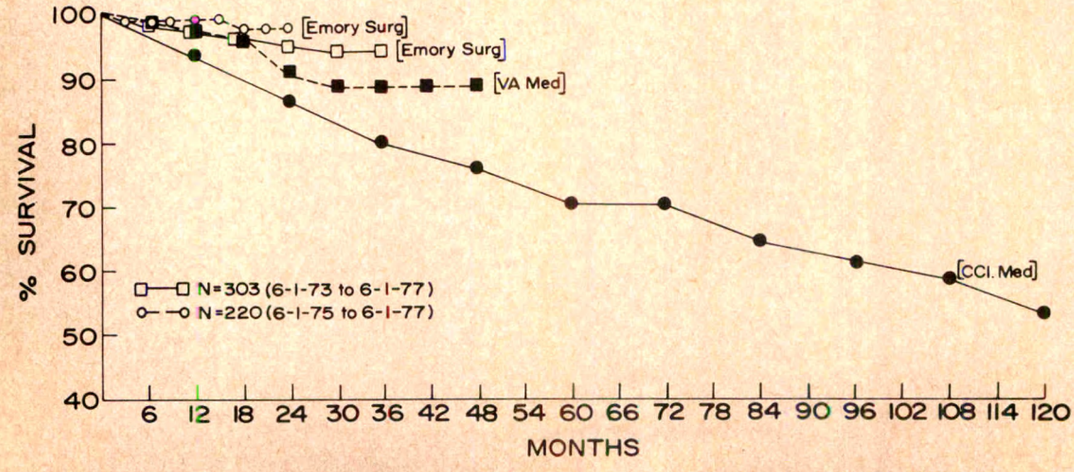

FIGURE 23. Survival curves of patients with double vessel obstruction treated medically at the Cleveland Clinic[24] (CCI. Med) (**lower curve**) and by the Veterans Administration group[51] (VA Med) (**black squares**) and treated with bypass surgery (surg) at Emory University Hospital between June 1, 1973 and June 1, 1977 (**open squares**) and between June 1, 1975 and June 1, 1977 (**open circles**). N = number of patients.

study. Thus, the difference in survival rates of these two medically treated groups is only 6 percent. Follow-up to 48 months shows a difference of only 11 percent. The cumulative survival rate at 36 months was 94 percent for the Emory surgical group; with improved surgical techniques of the past 2 years, the cumulative survival rate at 24 months is now 97 percent.

Single Vessel Obstruction

The medically treated patients with single vessel obstruction reported on by the Cleveland Clinic[24] had a 90 percent cumulative survival rate at 5 years (Fig. 2). Further examination of the group showed that the survival of patients with obstruction of the left anterior descending artery was poorer than for patients with obstruction of the circumflex or right coronary artery (Fig. 24). Figure 25 depicts the 5 year survival curve for patients who received bypass surgery at Buffalo General Hospital.[25] The cumulative survival rate for this surgical group was about 95 percent at five years compared with the cumulative survival rate of 82 to 88 percent in the five series of medically treated patients.

Kouchoukos et al.[9] found no difference in the survival curves of patients treated surgically and those treated

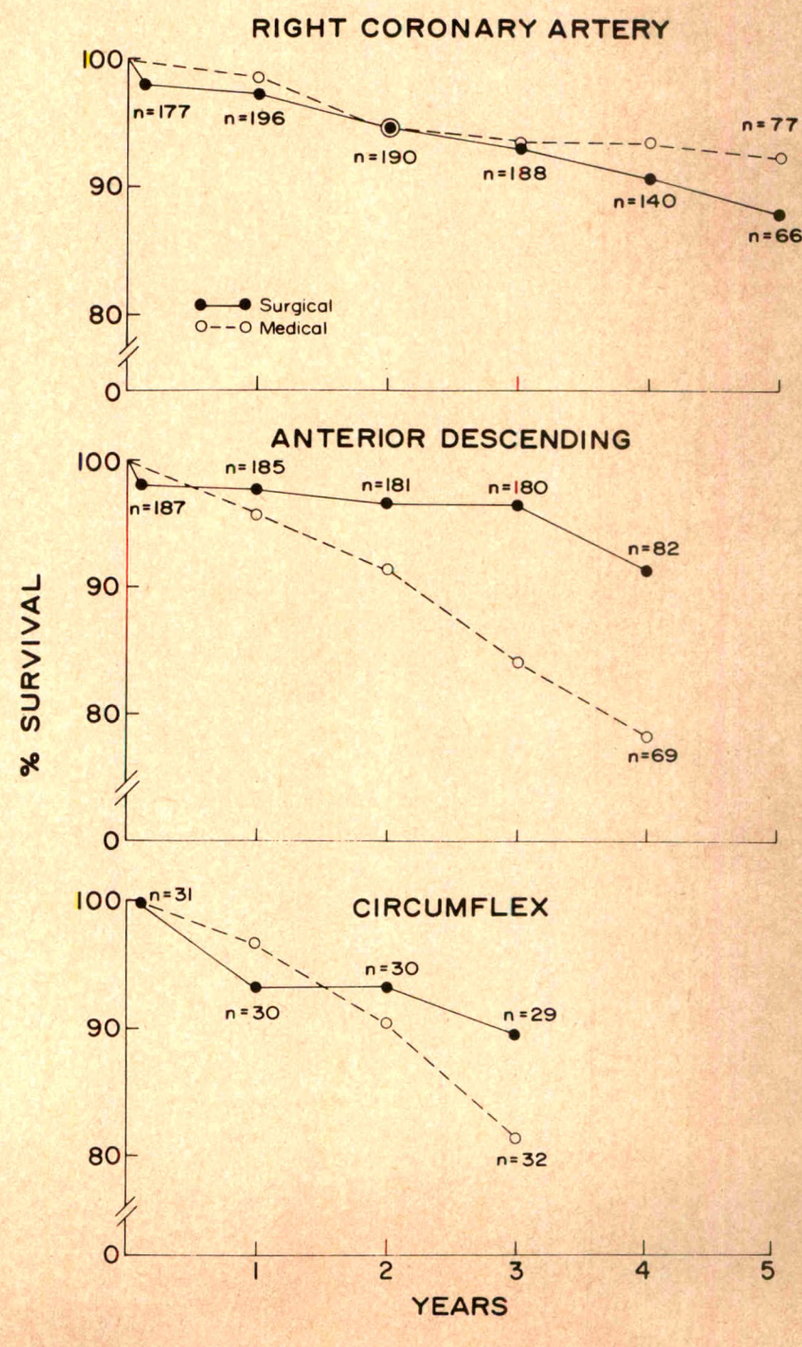

FIGURE 24. Five year survival curves of patients with single vessel obstruction of the right, left anterior descending or circumflex coronary artery treated medically (**curves connected with open circles**) and surgically (**curves connected with black circles**) at the Cleveland Clinic.[10] n = number of patients. (Reproduced with the permission of Sheldon et al.[10] and *Progress in Cardiovascular Disease.*)

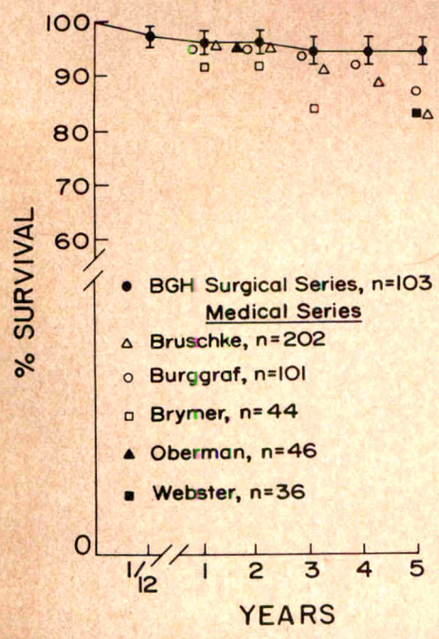

FIGURE 25. Survival curves of patients with single vessel disease who had bypass surgery at the Buffalo General Hospital (BGH) and of several series of medically treated patients.[26–31] n = number of patients. We thank David Greene and his colleagues[25] for permitting us to reproduce this graph.

medically. Hammermeister et al.[39] also found very little difference in survival of the two groups when the ejection fraction was normal. The cumulative survival rate was 98 percent at 4 years in the surgical group and 92 percent in the patients treated medically.

Kirklin et al.[37] found no difference between the survival curves of the Veterans Administration medical group and the University of Alabama surgical group and the survival curves of a group of persons from the general population who were matched for age, race and sex. Fortunately, the cumulative survival rate at 5 years was about 94 to 96 percent for both the surgically treated and medically treated patients.

Figure 26 shows the superimposition of the cumulative survival curves of medically treated patients reported on by Bruschke,[24] Brymer et al.[28] and Webster et al.[31]; medically treated patients reported on by the Veterans Administration of randomized patients with chronic stable angina pectoris,[51] patients in the Emory University Hospital 3 year follow-up study of patients with coronary bypass surgery who were operated on from June 1, 1973 to June 1, 1977, and patients operated on in the last 2 years of that study. The cumulative survival rate of the two surgical groups at Emory is about 98 to 99 percent; that of the groups treated medically and reported on by the Cleveland Clinic and Veterans Administration is about the same at the same time period. The Emory surgical groups fare slightly better than the groups reported by Brymer[28] and Webster[31] and their co-workers.

To date, there is no convincing evidence that coronary bypass surgery will improve the long-term survival of patients with single vessel obstruction. However, surgery is still indicated for patients with single vessel obstruction who have unacceptable angina pectoris. Patients do die of single vessel obstruction, especially obstruction of the left anterior descending artery, and infarction occurs and leads to disability although the patient does not die. More research is needed in this subset of patients. In the meantime, we agree with the conclusions of Abedin and Dack,[53] who wrote:

> For a single left anterior descending artery bypass, a competent surgical team should be able to achieve an operative mortality rate of less than 1%, a perioperative myocardial infarction rate of less than 4% and a patency rate of the bypass graft of more than 90%. Provided that such low morbidity and mortality rates can be achieved, it is logical to anticipate that surgical therapy will benefit a subgroup of symptomatic patients with an isolated proximal lesion of the left anterior

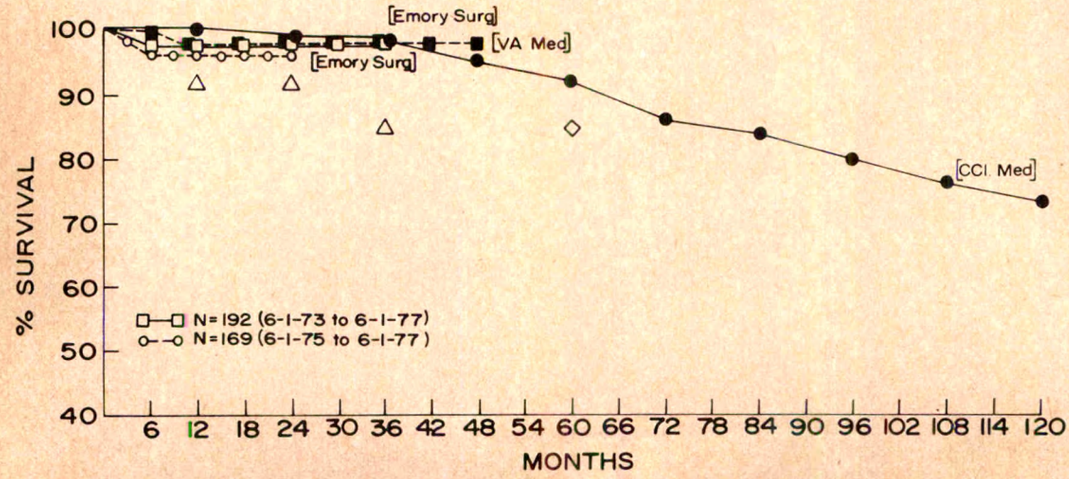

FIGURE 26. Survival curves of patients with single vessel obstruction treated medically at the Cleveland Clinic[24] (CCl. Med) (**lower curve**) and by the Veterans Administration group[51] (VA Med) (**black squares**), and treated with bypass surgery (surg) at Emory University Hospital from June 1, 1973 to June 1, 1977 (**open squares**) and from June 1, 1975 to June 1, 1977 (**open circles**) (see text).

descending coronary artery, without collateral vessels and with normally contracting myocardium in its distribution.

Discussion

Almost all patients who are operated on at Emory University Hospital have angina pectoris, and the majority of them have unstable angina. We do not delay or procrastinate when the proper mix of clinical indicators is present. These indicators include the amount of symptoms, the result of the exercise test (when it is not contraindicated), the extent and location of the coronary lesions as determined with coronary arteriography, the condition of the left ventricle as determined with left ventriculography, and the age and general health of the patient. We require more symptoms in older patients than in younger patients before recommending surgery.

We currently perform coronary bypass surgery on about 750 patients each year at Emory University Hospital. The overall operative risk is about 1.0 percent. The operative risk in certain subsets of patients with coronary disease is about 0.5 percent. The perioperative infarction rate is 4 to 6 percent. Most obstructing lesions are bypassed, and the graft patency rate is about 90 percent. These operative results make it possible for us to recommend surgical treatment in certain patients, whereas we would *not* recommend surgery for the same patient if the operative risk were 5 percent, the perioperative infarction rate were 12 percent; many lesions were not bypassed and 25 percent of the grafts closed.

Angina pectoris has been relieved or decreased in 92 percent of our patients who have had bypass surgery. Sixty-three percent of patients have had total relief of angina pectoris, 29 percent have had less angina, 5 percent have had the same amount as before operation and 3 percent have had more.

The preceding discussion compares the outcome of medically treated patients with that of surgically treated patients. The subsets of patients have generally been identified according to the location of the obstructing lesions and the status of left ventricular function. Most of the data reported here were derived from graphs. Accordingly, the figures given may vary one or two percentage points from the actual numbers. The survival rate of our surgically treated patients is compared with the survival rate of groups given the very best medical treatment available. Accordingly, a comparison of survival is made between the Emory surgical group with the Veterans Administration medical group of patients with left main coronary arterial obstruction as reported by Takaro et al.[42] The survival rates of patients with triple, double and single vessel obstruction treated surgically at Emory University Hospital are compared with those of the angiographically matched patients treated medically in the Veterans Administration trial as reported by Read et al.[51] Because the majority of patients operated on at Emory have had unstable angina pectoris and the patients in the Veterans Administration study had chronic stable angina pectoris, such a comparison should favor medical treatment. In fact, the comparison favored surgical treatment for all patients except those with single vessel obstruction.

Because coronary atherosclerotic heart disease is a very serious disease and the operative mortality is now about 1 percent in many medical centers, we prefer to state that patients with left main coronary arterial obstruction or triple or double vessel disease are more likely to have their life prolonged with properly performed bypass surgery than with medical therapy. McIntosh and Garcia[54] came to similar conclusions but stated them differently. They wrote that ". . . with the exception of left main coronary artery disease and possibly other subsets such as those with total occlusion of the right coronary artery and 70 percent but less than total occlusion of the left anterior descending coronary artery, there are inadequate data to justify the premise that [aortocoronary bypass grafting] prolongs life." From the addition of "[possible] other subsets" to the group with left main disease, it is obvious that McIntosh and Garcia are moving toward our positive statement that we have adequate evidence that bypass surgery prolongs the life of patients with left main coronary arterial obstruction and triple or double vessel obstruction but do not have adequate evidence that the procedure is superior to medical management in prolonging the life of patients with single vessel obstruction. The patients we subject to coronary bypass surgery are patients McIntosh and Garcia place in their exceptional group, those who ". . . have left main coronary artery obstruction and patients such as those with total occlusion of the right coronary artery and more than 70 percent but less than total occlusion of the left anterior descending coronary artery." The patients encompassed by their term "such as" will include those with triple or double vessel obstruction. Most of the patients operated on at Emory University Hospital have such lesions. Accordingly, we do not call them exceptional.

It seems proper to utilize *both* medical and surgical techniques in treating coronary atherosclerotic heart disease. There is powerful evidence that modern (especially since 1976) coronary bypass surgery relieves angina pectoris and prolongs life in properly selected patients. There is powerful evidence that medical management (especially the proper use of propranolol) decreases angina pectoris, and there is some evidence that it prolongs life. Because coronary bypass surgery produces its benefit by *increasing coronary blood flow* and because propranolol produces its benefit by *decreasing the oxygen requirement* of the myocardium, it seems wise to use both approaches in the same carefully selected patients.

References

1. **Miller DW Jr:** The Practice of Coronary Artery Bypass Surgery. In, Topics in Cardiovascular Disease (Sonnenblick E, Parmley WW, series ed). New York, Plenum Medical Book Company, 1977, p 1–231

2. **Peto R, Pike MC, Armitage P, et al:** Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. Br J Cancer 34:585–612, 1976
3. **Lovejoy EP:** Statistics for Math Haters. New York, Harper & Row, 1975, p 4
4. **Croxton FE:** Elementary Statistics with Applications in Medicine and the Biological Sciences. New York, Dover Publications, 1953, p 1–319
5. **Mundth ED, Austen WG:** Surgical measures for coronary heart disease. N Engl J Med 293:75–79; 124–129, 1975
6. **Hultgren HN, Peduzzi P, Pfeiffer JF, et al:** Medical versus surgical therapy for coronary artery disease—effect on symptoms. Presented at the Annual Meeting of the Association of University Cardiologists, Phoenix, Arizona, January 19, 1978
7. **Hutter AM Jr, Russell RO Jr, Resnekov L, et al:** Unstable angina pectoris. National randomized study of surgical vs medical therapy: results in 1, 2 and 3 vessel disease (abstr). Circulation 55, 56:Suppl III:III-60, 1977
8. **Siegel W, Lim HS, Proudfit WL, et al:** The spectrum of exercise tests and angiographic correlation in myocardial revascularization surgery. Circulation 52:Suppl I:I-156–I-162, 1975
9. **Kouchoukos NT, Oberman A, Karp RB:** Results of surgery for disabling angina pectoris. In, Coronary Bypass Surgery (Rahimtoola SH, ed) In, Cardiovascular Clinics (Brest AN, ed). Philadelphia, FA Davis, 1977, p 157–166
10. **Sheldon WC, Rincon G, Pichard AD, et al:** Surgical treatment of coronary artery disease: pure graft operations, with a study of 741 patients followed 3–7 yr. Prog Cardiovasc 18:237–253, 1975
11. **Vlietstra RE, Chesebro JH, Frye RL, et al:** Exercise hemodynamic improvement after aorta-coronary artery bypass surgery (abstr). Am J Cardiol 41:410, 1978
12. **Miller DW Jr, Dodge HT:** Benefits of coronary artery bypass surgery. Arch Intern Med 137:1439–1446, 1977
13. **Marco JD, Barner HB, Kaiser GC, et al:** Operative flow measurements and coronary bypass graft patency. J Thorac Cardiovasc Surg 71:545–547, 1976
14. **Lichtlen T, Morcetti T, Haller J, et al:** Post operative evaluation of myocardial blood flow in aorta to coronary artery vein bypass grafting using xenon-residue detection technique. Circulation 46:445–455, 1972
15. **Ormand J, Platt M, Mills L, et al:** Thallium 201 scintigraphy and exercise testing in evaluating the patients prior to and after coronary bypass surgery (abstr). Circulation 55, 56:Suppl III:III-131, 1977
16. **Sheldon WC:** Factors influencing patency of coronary bypass grafts. In, The First Decade of Bypass Graft Surgery for Coronary Artery Disease. An International Symposium, Cleveland Clinic Foundation, 1977, p 77
17. **Grondin CM:** Factors influencing graft patency. In, Ref 16, p 75
18. **Murphy ML, Hultgren HN, Detre K, et al:** Treatment of chronic stable angina: a preliminary report of survival data of the randomized Veterans Administration cooperative study. N Engl J Med 297:621–627, 1977
19. **Plotnick GD, Conti CR:** Unstable angina: angiography, short- and long-term morbidity, mortality and symptomatic status of medically treated patients. Am J Med 63:870–873, 1977
20. **Richards DW, Bland EF, White PD:** A completed twenty-five-year follow-up study of 456 patients with angina pectoris. J Chronic Dis 4:423–433, 1956
21. **Gazes PC, Mobley EM Jr, Faris HM Jr, et al:** Preinfarction (unstable) angina. A prospective study. Ten year follow-up: prognostic significance of electrocardiographic changes. Circulation 48: 331–337, 1973
22. **Friesinger GC:** Prognosis of coronary atherosclerotic heart disease, chap 62E. In, The Heart (Hurst JW, ed). New York, McGraw-Hill, 1978, p 1211–1215
23. **Sones FM:** Cine coronary arteriography, chap 33, In, The Heart (Hurst JW, Logue RB, ed). New York, McGraw-Hill, 1966, p 701–710
24. **Bruschke AV:** Ten year follow-up of 601 nonsurgical cases of angiographically documented coronary disease. Angiographic correlations. In Ref 16, p 107
25. **Greene DG, Bunnell IL, Arani DT, et al:** Long-term survival after coronary bypass surgery. Buffalo General Hospital, State University of New York, Brochure for exhibit at American Heart Association Meeting, Miami, 1977
26. **Bruschke AVG, Proudfit WL, Sones FM:** Progress study of 590 consecutive nonsurgical cases of coronary disease followed 5–9 years. I. Arteriographic correlations. Circulation 47:1147–1153, 1973
27. **Burggraf GW, Parker JO:** Prognosis in coronary artery disease: angiographic, hemodynamic and clinical factors. Circulation 51: 146–156, 1975
28. **Brymer JF, Buter TH, Walton JA Jr, et al:** A natural history study of the prognostic role of coronary arteriography. Am Heart J 88: 139–143, 1974
29. **McNeer JF, Starmer CF, Bartel AG, et al:** The nature of treatment selection in coronary artery disease: experience with medical and surgical treatment of a chronic disease. Circulation 49:606–614, 1974
30. **Oberman A, Harrell RR, Russell RO Jr, et al:** Surgical versus medical treatment in disease of the left main coronary artery. Lancet 2:591–594, 1976
31. **Webster JS, Moberg C, Rincon G:** Natural history of severe proximal coronary artery disease as documented by coronary cineangiography. Am J Cardiol 33:195–200, 1974
32. **Cohn LH, Boyden CM, Collins JJ:** Improved long-term survival after aortocoronary bypass for advanced coronary artery disease. Am J Surg 129:380–385, 1975
33. **Spencer FC, Isom OW, Glassman E, et al:** The long-term influence of coronary bypass grafts on myocardial infarction and survival. Ann Surg 180:439–451, 1974
34. **Lawrie GM, Morris GC Jr, Howell JF, et al:** Results of coronary bypass more than 5 years after operation in 434 patients: clinical, treadmill exercise and angiographic correlations. Am J Cardiol 40:665–672, 1977
35. **Lawrie GM, Morris GC Jr, Howell JF, et al:** Special correspondence: a debate on coronary bypass. N Engl J Med 297:1464, 1977
36. **Austen WG:** Personal communication, April 1978
37. **Kirklin JW:** Personal communication, April 1978
38. **Vlietstra RE, Assad-morell JL, Frye RL, et al:** Survival predictors in coronary artery disease: medical and surgical comparisons. Mayo Clin Proc 52:85–90, 1977
39. **Hammermeister KE, DeRouen TA, Murray JA, et al:** Effect of aortocoronary saphenous vein bypass grafting on death and sudden death: comparison of nonrandomized medically and surgically treated cohorts with comparable coronary disease and left ventricular function. Am J Cardiol 39:925–934, 1977
40. **Vismara LA, Miller RR, Price JE, et al:** Improved longevity due to reduction of sudden death by aortocoronary bypass in coronary atherosclerosis: prospsective evaluation of medical versus surgical therapy in matched patients with multi-vessel disease. Am J Cardiol 39:919–924, 1977
41. **Gunnar R:** Improved survival following surgical therapy in patients with chronic angina pectoris. A single hospital's experience in a randomized trial. Presented at the Annual Meeting of the Association of University Cardiologists, Phoenix, Arizona, January 19, 1978
42. **Takaro T, Hultgren HN, Lipton MJ, et al:** The VA Cooperative randomized study of surgery for coronary arterial occlusive disease. II. Subgroup with significant left main lesions. Circulation 54: Suppl III:III-107–III-117, 1976
43. **Lim JS, Proudfit WL, Sones FM Jr:** Left main coronary arterial obstruction: long-term follow-up of 141 nonsurgical cases. Am J Cardiol 36:131–135, 1975
44. **DeMots H, Bonchek LI, Rosch J, et al:** Left main coronary artery disease: risks of angiography, importance of coexisting disease of other coronary arteries and effects of revascularization. Am J Cardiol 36:136–141, 1975
45. **Cohen MV, Cohn PF, Herman MV, et al:** Diagnosis and prognosis of main left coronary artery obstruction. Circulation 45, 46:Suppl I:I-57–I-65, 1972
46. **Alford WC Jr, Shaker IJ, Thomas CS, et al:** Aortocoronary bypass in the treatment of left main coronary artery stenosis. Ann Thorac Surg 17:247–253, 1974
47. **Crochet D. Petitclerc R, Campeau L:** Left main coronary artery

stenosis: significance of degree of obstruction, associated involvement of other coronary arteries and of status of left ventricular contraction as related to surgery (147 cases) (abstr). Circulation 49, 50:Suppl III:III-111, 1974

48. **Sheldon WC:** Effect of bypass graft surgery on survival: a six to ten year follow-up study of 741 patients. In, Ref 16, p 127
49. **Goldberg S, Grossman W, Markis JE, et al:** Total occlusion of the left main coronary artery: a clinical, hemodynamic and angiographic profile. Am J Med 64:3–8, 1978
50. **Parker JO:** Prognosis in coronary artery disease: arteriographic, ventriculographic and hemodynamic factors. In, Ref 16, p 111
51. **Read RC, Murphy ML, Hultgren HN, et al:** Survival of men treated for chronic stable angina pectoris: a cooperative randomized study. J Thorac Cardiovasc Surg 75:1–16, 1978
52. **Lichtlen PR:** Natural history of coronary artery disease based on coronary arteriography, a critical review. In, Ref 16, p. 117
53. **Abedin Z, Dack S:** Isolated left anterior descending coronary artery disease: choice of therapy. Am J Cardiol 40:654–657, 1977
54. **McIntosh HD, Garcia JA:** The first decade of aortocoronary bypass grafting, 1967–1977: a review. Circulation 57:405–431, 1978

Influence of Myocardial Revascularization on Survival

Controversies in Cardiology: Part II

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Coronary bypass surgery can be performed with a low rate of morbidity and mortality and can successfully reduce or eliminate symptomatic angina pectoris. However, it is not yet clear whether the procedure prolongs life. A definitive answer to this question requires long-term prospective data on patients undergoing surgical or medical therapy who are comparable in degree of ventricular impairment, severity of symptoms and type and extent of coronary artery disease.

As the antagonist on the issue of whether myocardial revascularization procedures prolong life, let me say at the outset that I hope they do, but the evidence has not yet convinced me that they do, except in a special subset of patients with ischemic heart disease. There is no question in my mind that modern day coronary arterial surgery can be performed with a low operative mortality rate and a moderately low operative rate of myocardial infarction. In addition, successful bypass surgery will reduce or eliminate symptoms in patients suffering from angina pectoris. Every journal one sees contains a testimonial to this fact by one group or another. However, one cannot necessarily assume that a surgical procedure that can be performed safely is indicated or that it will prolong life by comparison with other types of therapy.

Comparability of Patients

One important aspect of studies dealing with medical and surgical treatment is: *comparability of patients.* In my view, to compare survival of patients with ischemic heart disease one should perform a prospective study of patients comparable in (1) degree of ventricular impairment, (2) severity of symptoms, and (3) extent of coronary artery disease.

Comparable patients is the key phrase when comparing survival data or any other end point. For example, all patients undergoing coronary surgery are surgical candidates by definition and therefore must have proximal coronary arterial stenosis, patent distal vessels and acceptable ventricular performance. The same should be true for the medically treated patients with whom they are compared.

Ventricular function: It is generally accepted that the degree of permanent ventricular impairment is the most important determinant of survival in medically treated patients. All published data indicate that patients with the same degree of coronary artery disease but with different degrees of ventricular impairment have different prognoses. Bruschke et al.,[1] Burgraff and Parker[2] and Gross et al.[3] have clearly shown that if the degree of ventricular impairment is small, survival can be favorably influenced in medically treated patients, even in those with multiple vessel coronary artery disease. Thus, it is unfair to compare results of modern cardiac surgery with results published in old "natural history" studies, many of which give no information about ventricular function or operability of coronary arterial vessels. In many instances there is no angiographic information at all.

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Symptoms: In addition to comparable anatomy and physiology, it is also important to consider the symptomatic state of the patient when assessing results of medical and surgical therapy. Most clinicians agree that patients with ischemic heart disease who are receiving intensive medical therapy but continue to have moderate or severe angina should be offered coronary bypass surgery. Relief of symptoms after surgery is astounding in this group of patients. However, there is no medical control group to compare with the surgical group because no one is willing to withhold symptomatic relief from these patients to test the hypothesis that surgery prolongs life. Thus, in my view, this is not the group that needs to be tested. To examine whether surgery does prolong life, patients with controlled or mild ischemic symptoms should be the group considered for surgery, because these are the patients in whom a therapeutic choice exists. So far, all of the random trials for stable angina and unstable angina compare surgical therapy with medically "controlled" patients.

Type of coronary artery disease: When comparing the effect of medical or surgical therapy on survival of patients with ischemic heart disease, one must further consider the extent, location and severity of coronary artery disease and their effects on prognosis. For example, the prognosis in the subset of symptomatic patients with left main coronary artery disease may differ from that of symptomatic patients with multiple or single vessel disease affecting other arteries.

Most will agree that data in the Veterans Administration Cooperative Trial indicates that surgery probably prolongs life in patients with angina pectoris resulting from left main coronary stenosis.[4] This study compares the survival data of 44 surgically treated and 46 medically treated patients and shows that the 4 year cumulative survival rate of 90 patients with left main coronary artery disease was significantly better in the surgically treated group. Thus, at present, surgery is the therapy of choice in this subset of patients with ischemic heart disease. Interestingly, some persons who support this interpretation of the Veterans Administration data fail to support the same group's observation that surgery does not necessarily prolong life in patients with symptomatic coronary artery disease that does not involve the left main coronary artery. I am not entirely clear why this should be the case.

All "natural history studies," random or otherwise, indicate that patients with ischemic heart disease secondary to single vessel coronary artery disease have a much better prognosis than patients with multiple vessel involvement.[2,4–6] In this subset of patients with ischemic heart disease, the data indicate that medical therapy is as good as surgical therapy when survival is considered the sole end point.

Multivessel disease: The prognosis in the third subset of patients with ischemic heart disease, symptomatic patients with multiple vessel disease, is less well defined than in the previous two subsets. This is the group in whom the clinical decision for medical or surgical therapy stirs up the most controversy. However, current data available in all of the trials on stable angina, in which comparable patients received medical or surgical therapy, indicate that there is no significant difference in the mortality at this point in the follow-up period. However, a significant difference in survival may emerge after several more years. The data obtained from the trials on stable angina are remarkably similar to the survival data obtained in the random trial for unstable angina, but the length of follow-up in both studies has been short, and a much longer period of assessment is required. Data published in the random trial reported by Bertolasi et al.[7] show a subgroup of patients with "progressive angina" whose survival is the same with medical or surgical therapy at 32 months.

Gross et al.[3] have recently provided reassurance that many patients rejected for operations and treated medically have a low mortality rate and can lead productive lives. Their data indicate that survival at 36 months is significantly greater in patients with an ejection fraction of more than 35 percent than in patients with a smaller ejection fraction, regardless of the degree of coronary vessel involvement.

Comparisons with survival data in normal population: In recent months it has become fashionable to compare surgical results in *selected* surgical centers with actuarial survival curves taken from the "normal population." It is impressive to see that in some centers survival curves of patients undergoing coronary surgery can almost be superimposed on those of the normal population at 4 and 5 years of follow-up. Several points have to be considered when making this type of comparison. First, the normal population contains many patients with a serious life-threatening illness (cancer of the lung, renal disease, hypertension, for example). In addition, it includes all of the patients who die suddenly, presumably as a result of ischemic heart disease. Patients who undergo cardiac surgery are selected from that patient population because they do not have life-threatening disease and in most instances have not experienced sudden near-death. It is known that most insurance companies are unwilling to recognize coronary surgery as a method of prolonging life at this time. After coronary bypass surgery patients pay the same insurance premiums as their medically treated counterparts with ischemic heart disease. Insurance companies argue that the current data base is too small to be statistically valid; that is, one cannot compare hundreds or thousands of patients undergoing operations with millions of the normal population. In addition, the insurance companies indicate that the evaluation of actuarial tables at age 50 requires up to 10 years of follow-up information to be statistically valid. In other words, adequate data are not yet available.

Although this method of analysis of survival data is interesting and may prove to be useful, it has not yet come of age. Perhaps if we could establish a national registry for all patients undergoing coronary bypass surgery, we might be able to determine our national mortality from coronary arterial surgery and compare that with actuarial tables from insurance companies.

Conclusions

In summary, I have tried to make the point that prognosis is different in different subsets of patients with ischemic heart disease. Thus, a prospective long-term study of *comparable* patients is necessary if meaningful data are to be obtained to answer the important question of whether myocardial revascularization prolongs life. Long-term, hard survival data comparing coronary surgery with medical therapy in comparable patients are not yet available. A few randomized studies to date have demonstrated no difference in survival between medically and surgically treated patients with single or multiple vessel disease. A significant improvement in survival has been shown for surgically treated patients with left main stem disease in a controlled study with a small number of patients. Uncontrolled studies have reported that patients with multiple vessel disease have improved survival with bypass surgery. This conclusion is not yet supported by the information available from published reports on controlled trials, although a longer follow-up period is required to fully evaluate the data.

Finally, I think it is well worth remembering that coronary bypass surgery does not exclude patients from continued medical therapy. Life-long medical care of all surgical patients is necessary and, if optimal medical therapy is continued after surgery, it should have a favorable influence on long-term surgical results.

References

1. **Bruschke AVG, Proudfit WL, Sones FM:** Progress study of 590 consecutive surgical cases of coronary disease followed 5–9 years. Ventriculographic and other correlations. Circulation 47:1154–1163, 1973
2. **Burggraf GW, Parker JO:** Prognosis in coronary artery disease. Angiographic, hemodynamic and clinical factors. Circulation 51: 146–156, 1975
3. **Gross H, Vaid AK, Cohen MB:** Prognosis in patients rejected for coronary revascularization surgery. Am J Med 64:9–20, 1978
4. **Read RC, Murphy ML, Hultgren HN, et al:** Survival of men treated for chronic stable angina pectoris. A cooperative randomized study. J Thorac Cardiovasc Surg 75:1–16, 1978
5. **Oberman A, Jones WB, Riley CP, et al:** Natural history of coronary artery disease. Bull NY Acad Med 48:1109–1125, 1972
6. **Webster JS, Moberg C, Rincon G:** Natural history of severe proximal coronary artery disease as documented by coronary cineangiography. Am J Cardiol 33:195–200, 1974
7. **Bertolasi CA, Tronge JE, Riccitelli MA, et al:** Natural history of unstable angina with medical or surgical therapy. Chest 70:596–605, 1976

LETTERS TO THE EDITOR

VETERANS ADMINISTRATION COOPERATIVE STUDY OF SURGERY FOR CORONARY ARTERIAL OCCLUSIVE DISEASE—I

We participated in the Veterans Administration cooperative study of surgery for coronary arterial occlusive disease for several years. It is a well designed and well performed study. However, it does not support the statement that "preliminary analysis of the data does not indicate that coronary arterial surgery improves survival in patients with single, double or triple vessel coronary artery disease and normal ventricular function."[1]

This study should be carefully intrepreted in the light of the selection process. The patients are preselected by their eligibility for Veterans Administration care and further selected by the rigid requirements of the study. A more accurate statement of the conclusions of this study is "preliminary analysis of the data does not indicate that coronary arterial surgery improves survival in men eligible for Veterans Administration care with stable angina for greater than 6 months. . .etc." These characteristics of the study population were acknowledged by the authors, although they considered the patient group to be similar to the group studied by McNeer et al.[2] at Duke University.

After we dropped out of the Veterans Administration study, we were responsible for two parallel open heart surgery programs, one at Wadsworth Veterans Administration Hospital and the other in a local community hospital. We have continued to follow up all patients carefully at 6 to 12 month intervals after surgery. Significant differences do exist between Veterans Administration and community hospital patients, both in preoperative characteristics and postoperative subjective response to surgery.[3] However, survival statistics from the surgically treated group at Wadsworth Veterans Administration Hospital during the years covered by the cooperative study (1972–1974) reveal a 2 year survival rate of 98 percent for *all* patients with three vessel disease (48 percent had abnormalities of left ventricular function). This figure compares favorably with the 90 percent 2 year survival rate for patients with three vessel disease and normal left ventricular function in the medically treated group in the Veterans Administration cooperative study. We dropped out of the cooperative study in part because it was clear to us that surgical care was not as carefully standardized as was medical care within the study group—perhaps in part because techniques were still evolving (indeed, rerandomization was begun in 1972 because of the high surgical mortality rate before that time). We do not believe that the surgical results of the Veterans Administration cooperative study are truly representative and believe that our results at Wadsworth over the same period support this conclusion.

The Veterans Administration cooperative study has merit as a study of the natural history of a highly selected group of men with chronic stable angina. Any conclusions regarding the merits of properly performed coronary bypass surgery in the population at large should be interpreted with extreme caution.

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References

1. **Detre K, Hultgren H, Takaro T:** Veterans Administration Cooperative Study of Surgery for Coronary Arterial Occlusive Disease. III. Methods and baseline characteristics, including experience with medical treatment. Am J Cardiol 40:212–225, 1977
2. **McNeer JF, Starmer CF, Bartel AG, et al:** The nature of treatment selection in coronary artery disease. Experience with medical and surgical treatment of a chronic disease. Circulation 49:606–614, 1974
3. **Carey JS, Cukingnan RA:** Subjective multivariable analysis for follow-up of coronary artery bypass. Arch Surg 111:769–772, 1976

REPLY

The major points of Carey and Cukingnan can be summarized as follows: (1) They are concerned that the results of our study should be interpreted as applicable only to patients who fulfill the entry requirements of the Veterans Administration study. (2) They have observed significant differences between Veterans Admistration and community hospital patients. (3) They challenge our preliminary results on lack of improved survival after surgery in the "low risk" group. (4) They state that poor standardization of surgery in the study prompted them to drop out of the collaborative study.

It is plainly stated in our Discussion that the Veterans Administration randomized study population is "not considered a random sample of men with stable angina pectoris. The patients were selected by: (1) their status as veterans, (2) their motivation and willingness to participate in the study, and (3) their ability to satisfy the comprehensive screening, arteriographic and inclusion criteria described." In spite of this, comparison of age, cardiovascular history, electrocardiographic and angiographic characteristics at entry indicated a remarkable similarity between the medical status of these patients and patients in the Duke study.

The comment on the significant differences between Wadsworth Veterans Administration and community hospital patients found by Carey and Cukingnan[1] refers to subjective reporting on improvement in symptoms after bypass surgery. This finding has no relevance to our present paper. Although the Wadsworth Veterans Administration patients reported not feeling as improved as the subjects in the community hospital following surgery, it remains to be proved that the surgical results were different by objective measures also. Most important, no evidence is given that these two groups of patients were comparable before surgery.

The 98 percent 2 year survival rate of the surgical patients in the Wadsworth Veterans Administration Hospital with three vessel disease is probably not different statistically (at an alpha = 0.05) from the 90 percent 2 year survival rate of the medical patients with three vessel disease and normal left ventricular function in the randomized Veterans Administration study. The randomized study had only 37 patients in that subgroup and the sample size for the Wadsworth Veter-

ans Administration Hospital, although not shown, could not have exceeded 50 patients because the entire 1972–74 cohort in the two Los Angeles hospitals consisted of only 188 patients.

The statement that the Wadsworth Veterans Administration Hospital dropped out of the Cooperative Study because the surgical care was less carefully standardized than the medical regimen does not correspond to our records. A communication from the hospital to the Cooperative Study Co-Chairman in March 1972 stated that disruption of facilities and personnel that followed "a natural disaster" made it impossible to continue the careful follow-up procedures required by the Cooperative Study protocol. (Only seven patients had been entered into the study up to that time.)

The criteria for performing the surgical procedures were carefully outlined in the study protocol. In addition, to ensure standardization of the surgical procedures a 2 day seminar was held at the Cleveland Clinic in May 1971 for all participating surgeons. The 5.6 percent overall 30 day hospital mortality rate after surgery for the years 1972–74, is not worse than what is reported from many other institutions[2–4] for that time period.

We agree with Carey and Cukingnan about the important effect that quality of surgery has on the treatment results. This is why we report on medical-surgical comparisons only for those subjects who entered the study between 1972–74.

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References

1. **Carey JS, Cukingnan RA:** Subjective multivariable analysis for follow-up of coronary artery bypass. Arch Surg 111:769–772, 1976
2. **Mathur VS, Guinn GA:** Prospective randomized study of coronary bypass surgery in stable angina: the first 100 patients. Circulation 51, 52: Suppl I:I-133–I-140, 1975
3. **Conley MJ, Wechsler AS, Anderson RW, et al:** The relationship of patient selection on prognosis following aortocoronary bypass. Circulation 55:158–163, 1977
4. **Bolooki H, Thurer RJ, Ghahramani A, et al.:** Objective assessment of aortocoronary bypass operation. Surgery 76:925–934, 1974

VETERANS ADMINISTRATION COOPERATIVE STUDY OF SURGERY FOR CORONARY ARTERIAL OCCLUSIVE DISEASE—II

Of particular interest to us in the report of the Veterans Administration cooperative study was the shape of the survival curve for those patients with obstruction of the left main coronary artery. We have taken the liberty of redrawing Figure 3 of that report with the percent survival on a logarithmic scale (our Fig. 1) and subjecting the resultant curves to exponential analysis. It is apparent from our figure that, with the exception of left main coronary disease, the survival curves are consistent with single exponentials having 50 percent survival times of 17.5 years, 13.8 years and 8.5 years for the "low risk," "all patients" and "high risk" groups, respectively. These figures would correspond to respective annual mortality rates of approximately 3, 5 and 9 percent.

However, the survival curve for those with left main coronary artery disease is best described by two exponentials rather than one. On the basis of this analysis, 75 percent of the patients in this group would adhere to an exponential with a half-time of 12 years (annual mortality rate 5.6 percent). This rate does not differ significantly from that derived from "all

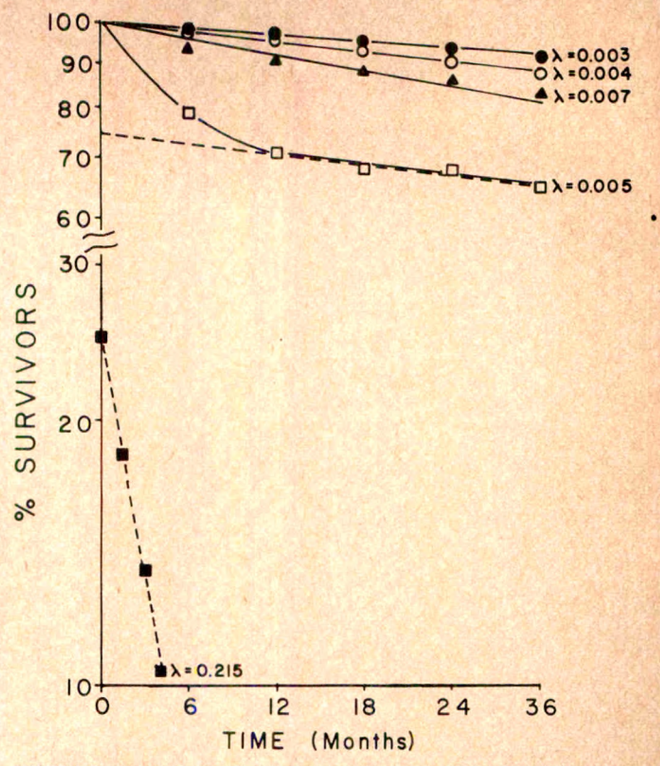

FIGURE 1. Survival data for patients with coronary disease, redrawn on a logarithmic scale from the data in Figure 3 of the report of the Veterans Administration Cooperative Study. Lines represent survival data for low risk **(closed circles),** all patients **(open circles),** high risk **(closed triangle)** and left main coronary disease **(open squares)** groups, respectively. A subgroup of the patients with left main coronary disease, calculated using the technique of exponential analysis from the data in the Veterans Administration report, is also shown **(closed squares).** The corresponding rate constants (λ) in months^{-1}, from top down, represent 50 percent survival times of 17.5 years, 13.8 years, 8.5 years, 12 years and 3.3 months.

patients." A much smaller group, 25 percent, is described by an exponential that defines a much worse prognosis, having a 50 percent mortality rate at only 0.27 years.

Although the use of exponential analysis for these data may be questioned, it does provide an explanation for the peculiar shape of the curve for left main coronary artery disease. Although this analysis was carried out on only a small number of patients, the data suggest at least two possible explanations:

1. Patients with left main coronary artery disease do not form a homogeneous group but consist of two subgroups at the time of angiography.

2. These patients constitute a homogeneous prognostically defined group, and the early high mortality rate reflects catheter-related deaths due to an acceleration in the occlusive process secondary to damage to the left main coronary artery during the procedure.

If the first explanation is true, then the majority (75 percent) of patients with left main coronary artery disease have a prognosis with medical management not significantly different from that of the mean of all patients with angina (only a 5.6 percent annual mortality rate). Only a small group (25 percent) would appear to have a very bad prognosis. We ask, therefore, if there is a subgroup among patients with left main coronary disease that requires further definition. If this interpretation is correct, the need for early surgical intervention in all patients with left main disease may not be justified on the basis of angiographic criteria alone.

The second explanation—which, if correct, would contraindicate angiography in these patients, might be clarified by detailed study of mortality data during the first 6 months after study, including autopsy reports.

We believe that these points require clarification before one can confidently recommend study of all patients with coronary heart disease and assignment of all patients with left main coronary disease to surgical management.

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REPLY

McCall and Katz raise the point that while the survival curves for all patients and for high and low risk patients without significant left main coronary arterial lesions in our Figure 3 fitted single exponential models, the survival curve of the patients with left main coronary artery disease was estimated to consist of a 3:1 mixture of two kinds of patients—one with a prognosis similar to that of all patients, with a median survival of 12 years, and a smaller group, with a very poor prognosis, having only a 3 month median survival time.

Although it is easy to see how these estimates were obtained by fitting two rather than one exponential survival models for the survival data of patients with left main coronary artery disease in our Figure 3, the most important scientific and practical questions still would be which, if any, clinical and angiographic entities would correspond to these extreme components?

Through extensive analyses, we were able to identify several subgroups of the total group with left main coronary artery disease which were at widely different risk of mortality. For example, Figure 4 shows in our report the survival of the patients with left main coronary artery disease with and without some left ventricular function abnormality. While the two survival rates are significantly different, survival in the subgroup with the better prognosis is still less than that of "all patients." A more extreme dichotomy can be obtained by adding the constraint of an ejection fraction of less than 50 percent which yields a small group of 15 patients whose median survival is 10 months. Compared with the results for all patients, the remaining patients are still at higher risk.

The estimated annual mortality rates and the median survival times of the decomposed group with left main coronary disease obtained by McCall and Katz are far from precise, as they are based on the observed survival rates of the small group with left main coronary disease (for example, 1 year survival rate and standard errors are 0.71 ±0.06). This being the case, the decomposed curves correspond quite well with the survival experience described in our earlier report[1] of the groups with left main coronary disease with an ejection fraction below or above 50 percent.

On the basis of all findings we agree with the first explanation of McCall and Katz, that the patients with left main coronary disease do not form a homogeneous group. (However, apparently single exponentials can also be generated by heterogeneous patient groups, as indicated by the curve for all patients in our Figure 3, which is the composite of all the other curves in the figure.) Their second explanation is interesting, but even if catheter-related acceleration of the occlusive process were a real possibility in left main coronary disease, how would one know whom to protect from angiography, as long as angiography is the primary method of diagnosing the disease?

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Herbert N. Hultgren, MD, FACC
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Reference

1. The Veterans Administration cooperative randomized study of surgery for coronary arterial occlusive disease. II. Subgroup with significant left main lesions. Circulation 54:Suppl III:III-107–III-117, 1976.

CONGESTIVE HEART FAILURE, CARDIOMEGALY AND EMBOLISM IN ISCHEMIC HEART DISEASE

Like an earlier pathologic study by Aberg[1] showing a relation between atrial fibrillation due to ischemic heart disease and systemic embolism, the recent study by Hinton et al.[2] failed to assess the independent roles of heart size and congestive failure. Can the authors tell us what the relation was between the presence of cardiomegaly or congestive failure, or both, and the presence of embolism in their patients with ischemic disease?

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References

1. **Aberg H:** Atrial fibrillation. I. A study of atrial thrombosis and systemic embolism in a necropsy material. Acta Med Scand 185:373–379, 1969
2. **Hinton RC, Kistler JP, Fallon JT, et al:** Influence of etiology of atrial fibrillation on incidence of systemic embolism. Am J Cardiol 40:509–513, 1977

REPLY

The incidence rate of congestive heart failure in patients with ischemic heart disease (our Table III) was approximately the same in those with atrial fibrillation (4 percent having severe, 21 percent slight or moderate congestive heart failure) as in those without atrial fibrillation (3 percent having severe, 28 percent slight or moderate heart failure), yet the incidence rate of embolism was 35 percent in those with and 7 percent in those without fibrillation. Congestive heart failure therefore appeared not to be a factor in the embolism. Heart size as such was not compared in the two groups with ischemic heart disease but, in the absence of valve disease, it should reflect the incidence of congestive heart failure and hypertension, and the latter was the same in the two groups. We reviewed our data on left ventricular hypertrophy (defined as left ventricular wall thickness of 14 mm or greater) and found this also to be roughly equal in these two groups with ischemic heart disease (86 percent of those with and 84 percent of those without atrial fibrillation).

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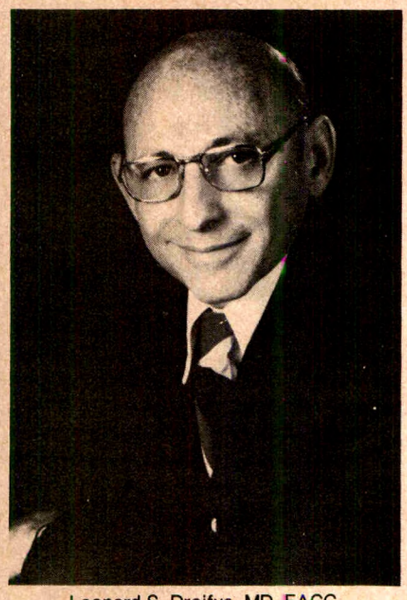

Leonard S. Dreifus, MD, FACC

President's Page: Membership Services

From its inception the American College of Cardiology has sponsored excellence in education and in the delivery of health care. As a result of continued growth and recognition, the College has become the principal spokesman for the cardiovascular specialist. This has mandated a rapid expansion in membership services. The diversity of our committees, task forces and activities brings into sharp focus the total involvement of the College and its members in the medical community.

The several goals and objectives adopted recently by the College membership, the Governors, Board of Trustees and Officers mandated that we become involved in the socioeconomic and regulatory affairs of our country in the interest of our membership, as well as patients. Initially the College assumed a low profile in these areas. In recent years we have been invited to play the role of consultants to various branches of government and to the health industry. Our counsel has always reflected well reasoned opinion in the best interest of cardiovascular care.

Within the past 3 years, the flurry of government interventions into the health care field has obligated the Board of Trustees and Officers of the College to respond promptly in every responsible way to the issues crucial to our membership. It is therefore relevant that I present an update of our activities with regard to federal health legislation and executive action. These issues, in my opinion, are of extreme importance to the membership of the College, and I urge every member to become knowledgeable about them and their far-reaching implications.

For example, the Department of Health, Education, and Welfare has recommended specific criteria for selected surgical procedures (including coronary arteriography) to the Professional Standards Review Organization (PSRO) Council. The Council has adopted these criteria, and the Bureau of Health Standards and Quality, Health Care Financing Administration has now instructed all PSROs to consider these criteria for screening patient care. The Bureau clearly states that these criteria are for subsequent physician review and do not constitute standards of care. The College is extremely concerned, however, that the exclusion criteria might actually be interpreted as mandatory criteria that would have the force of law.

The College has objected to the criteria that would permit coronary arteriography *only* for patients who are possible candidates for surgical revascularization. It has indicated that the best interest of patients is not served by excluding the use of coronary arteriography to evaluate the prognosis of patients who will not be candidates for surgical revascularization, assess new cases of uncomplicated angina or further examine asymptomatic patients with a positive stress electrocardiogram. It considers that there are certain circumstances in which coronary arteriography would be indicated: (1) in patients without a clear prognosis; (2) in patients with angina with a particularly impressive stress test; and (3) (rarely) in asymptomatic persons with a particularly impressive electrocardiographic response to stress. Furthermore, the College considers it unreasonable to administer large doses of beta blocking agents and long-acting nitrates to a patient who does not have a clearly established diagnosis of

angina. It also believes it unjustifiable to insist on a 3 week waiting period with intensive medical therapy before angiography can be performed in a patient with unstable or accelerating angina.

It is abundantly clear that the publication of criteria sets for mandating cardiovascular care will not stop here. The College must be in a position to respond quickly and effectively to these recommendations and regulations whenever they appear.

The Cardiovascular Norms Committee of the College has been particularly active in identifying optimal indications and standards for cardiovascular care. These must continually be updated to respond to the many inquiries of the federal agencies when indications and reimbursement decisions become an issue. Certain of the Interspecialty Advisory reports (such as those of the Inter-Society Commission for Heart Disease Resources [ICHD]) need immediate updating, and the College must play a major role in this process.

Through our Government Relations Committee and the prudent counsel of our legislative attorney, Raymond D. Cotton, Esq., the College has been extremely active in the following legislative areas:

I. Legislative Services

A. *Appropriations for the National Heart, Lung, and Blood Institute.*

The College has testified annually on appropriations for this vital Institute and, in so doing, has seen a 60 percent increase in federal funding of the Institute. At the same time, the College has developed an excellent rapport with the Institute, and with the House and Senate Labor-HEW Appropriations Subcommittees.

B. *Appropriations for the National Library of Medicine.*

The College has testified annually on appropriations for this important institution.

C. *Extension of Authorizations for the National Heart, Lung, and Blood Institute.*

For each of the last several years, the legal operating authorities of the National Heart, Lung, and Blood Institute have been scheduled to expire at the close of each fiscal year. The College has been called upon to testify, and to urge that these authorizations be sufficiently high to provide for expanded cardiovascular research and training opportunities and to stress the need for lengthier authorization extension periods.

D. *Medical Device Amendments.*

The College testified before and worked closely with both the Rogers and Kennedy Health Subcommittees in 1975 and 1976 to assure passage of a Medical Devices law that would regulate, but not impede, the scientific investigation of new devices.

E. *Health Manpower Legislation.*

Throughout 1975 and 1976, the College communicated its views to the pertinent Health Subcommittees regarding the impact of the Health manpower legislation on cardiovascular manpower and continuing medical education programs.

F. *National Institutes of Health Directors' Salaries.*

The College testified in 1976 and urged that the salaries of the Directors of the National Institutes of Health be substantially increased so as to encourage highly trained scholars and researchers to embrace these positions. The College position was adopted the following year by Congress.

G. *Federal Trade Commission Act Amendments.*

In 1977, Congress considered legislation that would have rendered nonprofit organizations, such as the College, subject to the jurisdiction of the Federal Trade Commission. The College, in its Congressional correspondence, noted that to subject such organizations to this jurisdiction and to the sanctions that it might have imposed (up to $10,000 per day fines) could have a devastating impact on the structure and the very existence of many nonprofit organizations. The noted amendment was subsequently eliminated from the legislation.

H. *Senate Nutrition Committee.*

Although the College position did not prevail, the College made efforts to urge Congress to extend, through 1978, the existence of the Senate Select Committee on Nutrition and Human Needs.

I. *Pending Issues.*

The Government Relations Committee and Mr. Cotton are currently in the process of delineating those issues raised by pending legislation that could have impact on the interests of the College. Appropriate correspondence or testimony to the following bills include: S.2755, which would overhaul the Federal Food, Drug and Cosmetic Act; S.2410, which would establish a National Institute of Health Care Research.

II. Federal Agency Services

It is mandatory that the College research, monitor and analyze important federal health agency activities and render advice on applicable programs, grants, procedures, contracts, rules and regulations. Reports and analyses, together with suggestions for action, are made to the College by our legal counsel. In recent years, the College has represented the interests of the membership by submitting to federal agencies formal "comments" on particular issues. Advice has also been provided directly to federal health program officials. The following are a few examples:

A. *National Guidelines for Health Planning.*

In September 1977, the Health Resources Administration (HRA) published, pursuant to the health planning law (P.L. 93-641), proposed guidelines governing institutional open heart surgery and cardiac catheterization unit services. The College submitted detailed comments on a number of issues raised by these guidelines. HRA then published a revised set of proposed guidelines, to which the College also submitted comments. The final National Guidelines for Health Planning, published in March 1978, embodied several of the suggestions raised by the College's document.

B. *Medical Devices.*

In August 1976, the Federal Food and Drug Administration published proposed regulations governing Investigational Device Exemptions. The College submitted formal comments delineating the manner in which these regulations would hinder investigation of medical devices.

C. *Ultrasound.*

For the last several years, the College has been monitoring the extent to which the federal government reimburses for ultrasonographic procedures performed on Medicare patients. At present, Medicare pays 80 percent of the reasonable charge whether the procedure is performed by a radiologist or a cardiologist. The radiology lobby has perennially urged that the policy be changed to allow 100 percent reimbursement for such procedures performed by a radiologist. The College, in working closely with the Social Security Administration, has thus far been

able to stave off this inequitable change in policy.

D. *Sponsors and Monitors of Drug Studies.*

In September 1977, the Food and Drug Administration published proposed regulations governing "The Obligations of Sponsors and Monitors of Clinical Investigations." The College, as part of the American College of Cardiology—American Heart Association Joint Advisory Committee on Cardiovascular Drugs, submitted comments to the Food and Drug Administration suggesting amendments to the proposed regulations that would impose less on the academic freedom of investigators.

E. *Nonclinical Laboratory Studies.*

The College also submitted comments in March 1977 in response to the publication of proposed rules governing "Good Laboratory Practice in Nonclinical Laboratory Studies." Final regulations have not yet been republished.

F. *Comments to the Board of Motor Carrier Safety.*

In 1977, the College submitted comments to the Board of Motor Carrier Safety, Federal Highway Administration urging amendment to proposed rules governing the licensure of truck drivers with a history of cardiovascular disease.

G. *Pending Issues.*

New sets of National Guidelines for Health Planning will be promulgated in the coming months and will probably be deserving of College review and comment. "Interim-Final Regulations" regarding Investigational Device Exemptions have been published, and formal comments are being prepared. The Medicare Bureau may, in the coming months, publish proposed regulations governing changes in reimbursement policy for ultrasonic procedures. The College will be meeting with Medicare officials before that time and will submit formal comments, if necessary.

Future Directions

If the College is truly to serve its members, we must become actively involved in all phases of our health care delivery system and the federal regulatory agencies that could compromise our professional effectiveness. The responsible opinion of the College has been extremely influential in the delivery of cardiovascular care in this country. In the future, the College must deal with the questions of training, manpower, licensure, certification, standards and reimbursement. I urge all members of the College to become knowledgeable and involved in the socioeconomic affairs of health care and to offer their imaginative comments as we shape future policies of our College.

Leonard S. Dreifus, MD, FACC
President
American College of Cardiology

28th ANNUAL SCIENTIFIC SESSION
AMERICAN COLLEGE OF CARDIOLOGY

Miami Beach, Florida **March 11–15, 1979**

- **Abstracts**
  Entries must be postmarked no later than September 18, 1978
- **Technical Exhibits**
  Deadline for requests for space: October 2, 1978
- **Scientific Exhibits**
  Deadline for requests for space: October 2, 1978
- **Young Investigators' Awards Competition**
  Entries must be postmarked no later than November 1, 1978

For application forms, write Patrick A. Ziarnik, Director, Annual Scientific Session Department, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

New Members

The following individuals were elected to membership in the American College of Cardiology on March 5, 1978 in the category indicated.

FELLOWSHIP

CADIGAN, Robert A., MD, Washington, DC
DIENEL, Nicholas Hans, MD, Medford, OR
DONOHUE, Dennis J., MD, Washington, DC
FELTER, Harold George, Jr., MD, Ft. Sam Houston, TX
HERRON, Robert Thomas, DO, St. Louis, MO
HOROWITZ, Leonard N., MD, Philadelphia, PA
LOGSDON, John Robert, MD, Ft. Sam Houston, TX
MADDOUX, Gerry L., MD, Albuquerque, NM
RAPHAEL, Lawrence David, MD, CM, San Bernardino, CA
SCHWARTZ, Michael A., MD, Lynn, MA

ADVANCE TO FELLOWSHIP

KLUGE, Wolfgang F., MD, Seattle, WA

The following individuals were elected to membership in the American College of Cardiology on May 25, 1978 in the category indicated.

FELLOWSHIP

ABEDIN, Zainul, MBBS, Champaign, IL
ALAM, Samir E., MD, New York, NY
ALEXANDER, James A., MD, Gainesville, FL
ALTSCHULER, Harold, MD, Ft. Lauderdale, FL
ANSELMO, Paul J., MD, Los Angeles, CA
ASAPH, James W., MD, Portland, OR
BARATTA, Frank G., MD, Ft. Lauderdale, FL
BHARADWAJ, Baikunth B., MBBS, Saskatoon, Canada
BLAIS, Robert E., MD, Ft. Lauderdale, FL
BLOOD, David K., MD, New York, NY
BORER, Jeffrey S., MD, Bethesda, MD
BORKAT, Gordon, MD, Cleveland, OH
BRAMOWITZ, Alan D., MD, Pittsburgh, PA
BROWN, Patrick L., MD, Huntington, WV
CANDELA, Richard J., MD, Columbus, OH
CANTOR, Stephen A., MBBS, Oakland, CA
CHANIOTIS, Lambros, MD, Pointe-Claire, Canada
CHIOTELLIS, Philip N., MD, Hyannis, MA
CHUNG, George Kau Jai, MD, Honolulu, HI
COHEN, Howard A., MD, Bethesda, MD
COHEN, Howard L., MD, Huntington, NY
COWLEY, Michael J., MD, Richmond, VA
CUMMINS, Frank E., MD, Milwaukee, WI
DASHKOFF, Neil, MD, Buffalo, NY
DICKINSON, William A., Jr., MD, Virginia Beach, VA
DOROSTI, Khosrow, MD, Cleveland, OH
DOSHI, Ashokkumar M., MBBS, Chicago, IL
DREWS, John A., MD, Orange, CA
FISHER, Gary P., MD, Chevy Chase, MD
FRANCIS, Charles K., MD, Hartford, CT
FRIEDEMAN, Sanford J., MD, New York, NY
FULTON, Robert L. MD, Louisville, KY
FUSTER, Valentin, MD, Rochester, MN
FYE, W. Bruce, MD, Marshfield, WI
GIESEKE, William D., MD, Ft. Lauderdale, FL
GOLDSMITH, Stanley J., MD, New York, NY
GREEN, Edward W., MD, Detroit, MI
GUTGESELL, Howard P., MD, Houston, TX
HIGGINS, Thomas G., MD, Short Hills, NJ
HIRSCHFELD, Stephen S., MD, Cleveland, OH
HOFFMAN, Julien I.E., MB, BCh, San Francisco, CA
HOLMES, David R., Jr., MD, Bethesda, MD
HOSHINO, Shunichi, MD, Fukushima, Japan
JAZAYERLI, Nabil, MD, Wichita, KS
JOHNSON, Gregory L., MD, Lexington, KY
KAFI, Ali, MD, Warren, MI
KATZ, Richard A., MD, La Mesa, CA
KAWAMURO, Kenzo, MD, Kalamazoo, MI
KENNEL, Arthur J., MD, Rochester, MN
KHAN, Jamal H., MBBS, Charleston, WV
KHAN, Mohammad Z., MBBS, Charleston, WV
KIRMSER, Ralph J., MD, Andrews AFB, MD
LABABIDI, Zuhdi, MD, Columbia, MO
LEE, Benny Chen Chu, MD, Visalia, CA
LEE, Tyan Y., MD, Fontana, CA
LESSER, Milton E., MD, Miami Beach, FL
LITCHFORD, Julian Brittian, MD, San Diego, CA
LOMBARDI, Anthony C., MD, Wilmington, DE
MAU, Richard D., MD, Anaheim, CA
McCARREN, Peter, MD, Albuquerque, NM
McNEER, James F., MD, Durham, NC
MIAN, Khalid A., MBBS, Kalamazoo, MI
MOGTADER, Allen H., MD, New York, NY
MORISSETTE, Martin-Paul, MD, Montreal, Canada
MORRIS, Douglas C., MD, Atlanta, GA
MORRISS, Mary Jeanette Hagan, MD, Houston, TX
NEWFELD, Edgar A., MD, Dallas, TX
OTERO, Jorge E., MD, Tampa, FL
PANEBIANCO, Antonio C., MD, Allentown, PA
PARK, Joon Myung, MD, Lubbock, TX
PATEL, Indravadan I., MBBS, Fairmont, WV
PATTERSON, Randolph E., MD, New York, NY
PIERONI, Daniel R., MD, Buffalo, NY
PRIOR, Michael W., MD, Providence, RI
RAJA, Kumar S., MBBS, Huntington Beach, CA
RANGANATHAN, Narasimhan, MBBS, Toronto, Canada
RANKIN, Larry S., MD, Carlisle, PA
RICH, Gary M., MD, Mobile, AL
RICHTER, Mary Ann, MD, New Orleans, LA
ROBERTS, Douglas L., MD, Buffalo, NY
ROLSTON, William A., MD, Metairie, LA
ROULEAU, Jacques R., MD, Quebec, Canada
SCHMIDT, Paul E., MD, Indianapolis, IN
SCHNEE, Mortimer A., MD, Somerville, MA
SHERMAN, Mark M., MD. Springfield, MA
SHINE, Kenneth I., MD, Los Angeles, CA
SHIROFF, Robert A., MD, Las Vegas, NV
SILVERMAN, James F., MD, Stanford, CA
SIMONYI, Janos, MD, Budapest, Hungary
SINGHAL, Shiam S., MD, Kanpur, India
SORDAHL, Louis A., PhD, Galveston, TX
SPOTNITZ, Henry M., MD, New York, NY
SRIDAROMONT, Somkid, MD, Lubbock, TX
STALLER, Bernard J., MD, Milwaukee, WI
STEGALL, Frank D., MD, Rome, GA
STEIN, Richard A., MD, Brooklyn, NY
STEIN, William G., MD, New York, NY
TERRY, Donald F., MD, Wichita Falls, TX
THEROUX, Pierre, MD, Montreal, Canada
THORNTON, Thomas G., MD, Dayton, OH
VANDER SALM, Thomas J., MD, Worcester, MA
VINE, Donald L., MD, Lexington, KY
VLODAVER, Zeev A., MD, Fridley, MN
WAY, Gerald L., MD, Denver, CO
WEISZ, Daniel, MD, New Hyde Park, NY
WELLS, James L, Jr., MD, Orangeburg, SC
WESTCOTT, R. Jeffrey, MD, Seattle, WA
WILLIAMS, Edward H., MD, Galveston, TX
WILLIAMSON, John S., MD, Ft. Dix, NJ
WILLIAMSON, Michael D., MD, Clearwater, FL
WRIGHT, Philip W., MD, Long Beach, CA
YABEK, Steven M., MD, Albuquerque, NM
YAP, Jose I., MD, East Detroit, MI

ADVANCE TO FELLOWSHIP

AINTABLIAN, Agop, MD, New Hyde Park, NY
ALAM, Mohsin, MBBS, Detroit, MI
ALTER, Barry R., MD, Ft. Sam Houston, TX
ANDERSON, Richard A., MD, Portland, ME
ASATO, Hiroaki, MD, Morgantown, WV
AWDEH, Mahir R., MD, Memphis, TN
BAGA, Victor B., MD, Venice, FL
BHATT, Dilip R., MD, Fontana, CA
BISHOP, William B., MD, Little Rock, AR
BUTTROSS, David, Jr., MD, Lake Charles, LA
CALL, Thomas D., MD, Norfolk, VA

CANTO, Jose D., MD, South St. Paul, MN
CASSIDY, John, MD, Whittier, CA
CHADDA, Kul D., MBBS, Brooklyn, NY
CHEN, Mao-Hsiung, MB, Columbus, OH
CHEUNG, Ming-Tat, MB, Weston, Canada
CRELINSTEN, Gordon L., MD, CM, Montreal, Canada
CUMMINGS, James M., MD, Kansas City, KS
DEEDWANIA, Prakash C., MBBS, Salem, VA
DEGLIN, Stuart M., MD, Morgantown, WV
DENNISH, George W., III, MD, San Diego, CA
DIETTERT, Gerald A., MD, Missoula, MT
EDMISTON, W. Allan, Jr., MD, Los Angeles, CA
ESKIN, David J., MD, Abington, PA
FOX, Martin, MD, Stamford, CT
FRIEDEWALD, Vincent E., Jr., MD, Honolulu, HI
FRIEDLI, Beat, MD, Geneva, Switzerland
GASH, Arnold K., MD, Biloxi, MS
GAY, John H., MD, Des Moines, IA
GORSUCH, Thomas L., MD, Waynesboro, VA
GOZO, Edilberto G., Jr., MD, Cebu, Philippines
GRABOYS, Thomas B., MD, Boston, MA
GUPTA, Satyendra C., MBBS, Dayton, OH
HA-UPALA, Santa, MD, Bangkok, Thailand
HENDERSON, John C., MD, Searcy, AR
HOCHE, John P., MD, New York, NY
ISHIMORI, Tetsuo, MD, Houston, TX
KIHNAL, Vithal, MD, Allen Park, MI
KRAJCER, Zvonimir, MD, Houston, TX
KRANTZ, Alexander P., MD, Lynwood, CA
LIPSKI, Janet I., MD, New York, NY
LUNDSTROM, Robert J., MD, Pacifica, CA
MAUTNER, Richard K., MD, New Orleans, LA
MAYTIN, Orlando, MD, Plantation, FL
MESETE, A. Francis, MD, Media, PA
MILLER, Gordon C., MD, Columbus, GA
MISRA, Kabi P., MD, Madras, India
NISHIMURA, Akira, MD, Galveston, TX
PALACIO, Alfredo, MD, Guayaquil, Ecuador
PALACIOS-MACEDO, Xavier, MD, Mexico, Mexico
PIRZADA, Farouk A., MD, Winchester, MA
POLINER, Lawrence R., MD, Dallas, TX
PORKOLAB, Frederick L., MD, Pittsburgh, PA
RAINES, Richard D., MD, Tulsa, OK
RAVINDRA, Nathan M.P., MBBS, Staten Island, NY
RICCI, Donald R., MD, San Diego, CA
ROTSZTAIN, Alberto, MD, Silver Spring, MD
SANMARTIN, Jorge E., MD, Omaha, NE
SCARPA, William J., MD, Brooklyn, NY
SCHNEE, Mark J., MB, ChB, Houston, TX
SEIN, Koung, MD, Glendale, CA
SHAHAWY, Mahfouz El, MD, Sarasota, FL
SIRAGUSA, Vincent, MD, Las Vegas, NV
SMITH, Ballard F., Jr., MD, Bradenton, FL
SUNDARARAJAN, Venkatesan, MBBS, Tamil Nadu, India
UNGER, Allen H., MD, New York, NY
URRUTIA, Luis E., MD, San Salvador, El Salvador
WALKER, John A., MD, Milwaukee, WI
WANDERMAN, Nancy-Ann C., MD, Charleston, WV
WISE, Joe R., Jr., MD, Bangor, ME
WYNNE, Joshua, MD, Boston, MA
YATES, Robert C., MD, Albany, NY
YEOMAN, Mark A., MD, Houston, TX
ZGLINIEC, Lawrence J., MD, Pontiac, MI
ZIMMER, Lawrence, MD, Cincinnati OH
ZUREIKAT, Harran Y., MD, Amman, Jordan

ASSOCIATE FELLOWSHIP

ABDULLAH, Johan, MBBS, Singapore, Singapore
AGSTER, Bruce E., MD, West Reading, PA
BERKOBEN, John P., MD, Newton, MA
BILLETTE, Jacques, MD, PhD, Montreal, Canada
BOKESCH, Charles R., MD, Mt. Airy, NC
BOLADO-RETANA, Enrique, MD, Sonora, Mexico
BOROOMAND-RASHTI, Kayoomars, MD, Kingston, Canada
CARRILLO-LOPEZ, Lauro, MD, Mexico, Mexico
FARHAD, Mohammad, MD, Esfahan, Iran
FLESSAS, Athanasios, MD, Dorchester, MA
FRANK, Stewart Lee, MD, San Diego, CA
FRICKER, Frederick J., MD, Pittsburgh, PA
GEY, George O., Jr., MB, BCh, Seattle, WA
HACKSHAW, Barry T., MD, Winston-Salem, NC
HARRIS, Allan H., MD, Cleveland, OH
HATFIELD, Kenneth B., MD, Chicago, IL
HOPKINS, Christie B., MD, Columbia, SC
KLEINBERG, Martha, V., MD, Toledo, OH
MAREK, Michael S., MD, Hollywood, FL
MAYMONE-MARTINS, Fernando A., MD, Lisbon, Portugal
MORALES, Dante D., MD, Rizal, Philippines
NARAHARA, Kenneth A., MD, Dallas, TX
NIMOITYN, Benjamin S., MD, Philadelphia, PA
PADNICK, Marvin B., MD, Manhasset, NY
PERRIGO, Earl S., MD, Oregon, OH
PORTER, Co-Burn J., MD, APO, New York, NY
PRITCHARD, David A., MBBS, Rochester, MN
RAPACZ, Raymond J., MD, La Grange, IL
SCHISANO, Denis S., MD, Berkeley Heights, NJ
SHETH, Mohit K., MBBS, Madisonville, KY
SWARTZ, Mark H., MD, New York, NY
THIND, Surinder S., MBBS, Benton Harbor, MI
TSE, Tak-Fu, MBBS, Hong Kong, Hong Kong
USMAN, Muhammad, MBBS, Brooklyn, NY
VARGAS-BAEZA, Joaquin A., MD, Veracruz, Mexico
WAHEED, Abdul, MBBS, Dallas, TX
WENZKE, Frank J., MD, Dayton, OH
YEN, Ya-Tang, MD, Elizabeth, NJ

ADVANCE TO ASSOCIATE FELLOWSHIP

HABIBZADEH, Mohammad A., MD, Phoenix, AZ
NABI, Aziz H., MD, Schenectady, NY
PITT, William A., MD, San Diego, CA
SARMA, Radha J., MBBS, Duarte, CA
SCHWARTZ, Richard A., MD, McLean, VA

AFFILIATE

ANTONIO, Felicitas S., MD, Jersey City, NJ
BAKER, George G., MD, Portland, OR
BARODDY, Naseeb B., Jr., MD, Florence, SC
COLE, John P., MD, Long Beach, CA
HUMPHREY, Steven B., MD, Van Nuys, CA
PADMANABHAN, Madras K., MD, Mission Hills, CA
PORTOS, Jose M., MD, Mexico, Mexico
SOTIRAKIS, Ivicos, MD, New York, NY
SOUNDARARAJAN, T.S., MBBS, Long Beach, CA
VILLAMIL, Ramon J., MD, Bluffton, IN
ZAVANELLA, Claudio, MD, Buffalo, NY

CALENDAR OF EXTRAMURAL PROGRAMS

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Extramural Programs Department, Division of Continuing Education, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

AUGUST 1978 THROUGH OCTOBER 1978

To be arranged individually Preceptorships in Cardiology. Arthur Selzer, FACC, director, Pacific Medical Center, San Francisco, CA

AUG. 26–28 **Tutorials in the Tetons: Cardiac Emergencies (Fourth Annual).** Robert S. Eliot, FACC, director and Alan D. Forker, FACC, William P. Nelson, FACC and Gerald L. Wolf, co-directors. Jackson Lake Lodge, Moran, WY

SEPT. 7–9 **The Clinical Pharmacology of Cardiovascular Drugs.** William B. Abrams, FACC, Albert N. Brest, FACC, Richard O. Davies, FACC and Roger F. Ferguson, co-directors. Marriott Motor Hotel, Philadelphia, PA

SEPT. 11–14 **Electrocardiography: Core Curriculum and Self-Assessment.** Paul L. McHenry, FACC, director and Charles Fisch, FACC, co-director. Myers Auditorium, Wishard Memorial Hospital, Indiana University Medical Center, Indianapolis, IN

SEPT. 11–14 **Electrocardiography: Core Curriculum and Self-Assessment.** Arthur Selzer, FACC, director. Golden Gateway Holiday Inn, San Francisco, CA

SEPT. 27–29 **Advanced Echocardiography.** Harvey Feigenbaum, FACC, director and Betty C. Corya, James C. Dillon, FACC and Arthur E. Weyman, FACC, co-directors. Indianapolis Hilton Hotel, Indianapolis, IN

OCT. 12–14 **Cardiology Update—1978.** William W. Parmley, FACC and Kanu Chatterjee, FACC, directors. Del Monte Hyatt House, Monterey, CA

OCT. 13–14 **Geriatric Cardiology. Physiologic vs. Pathologic Aging of the Cardiovascular System: Clinical Applications and Therapeutic Considerations.** Borys Surawicz, FACC and Raymond Harris, FACC, directors. Hyatt Regency Lexington, Lexington, KY

OCT. 18–20 **Cardiac Pacing.** Doris J. W. Escher, FACC and Seymour Furman, FACC, directors. Waldorf-Astoria Hotel, New York, NY

OCT. 19–21 **Valvular Disease—Practical Diagnosis and Management.** Peter C. Gazes, FACC, director and Charles P. Summerall III, FACC, Grady H. Hendrix, FACC, William H. Barnwell II, FACC, Bruce W. Usher, FACC, J. Lindsay Leviner, Jr. and Robert G. Irvin, co-directors. Kiawah Island Inn, Kiawah Island, Charleston, SC

LEARNING CENTER: PROGRAM CALENDAR

The American College of Cardiology's newest department, the Learning Center, located at the College's Bethesda, Maryland headquarters, began operations last October with the offering of its first continuing medical education program for physicians with a specialty or an interest in cardiovascular medicine. The purpose of the Learning Center is to support the professional commitment to quality patient care by providing a new standard of excellence in cardiovascular continuing education. For additional information concerning the programs listed below or for a complete schedule of programs through December 1978, contact Program Coordinator, Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014 (301) 897-5400.

AUGUST THROUGH DECEMBER 1978

Month/Dates	Course Director	Title of Program
August 7–10	R. Joe Noble, MD, FACC	**Update in Cardiology**
September 25–27	Kenneth M. Rosen, MD, FACC	**Evaluation of Arrhythmias with His Bundle Recording and Cardiac Stimulation**
October 4–6	Charles E. Rackley, MD, FACC	**Clinical Evaluation and Treatment of Coronary Artery Disease**
October 19–21	Pravin M. Shah, MD, FACC	**Adult Echocardiography: Clinical Applications–M-Mode vs 2-Dimensional**
October 23–25	Douglas P. Zipes, MD, FACC	**The Ubiquitous PVC: Sorting Out the Dilemma**
November 6–8	Ralph Shabetai, MD, FACC	**Management of Pericardial and Myocardial Disease**
December 4–6	Borys Surawicz, MD, FACC	**Interpretation of ECGs**
December 11–13	Victor Parsonnet, MD, FACC	**Current Concepts in Pacing: An Individualized Seminar Approach**

28th ANNUAL SCIENTIFIC SESSION
AMERICAN COLLEGE OF CARDIOLOGY

MARCH 11–15, 1979 MIAMI BEACH, FLORIDA

AMERICAN COLLEGE OF CARDIOLOGY

Announces . . .

AFFILIATE IN TRAINING MEMBERSHIP

For Physicians in Cardiovascular Related Training Programs

Candidates for this membership category must be current full-time trainees in a recognized cardiovascular (adult, pediatric, surgical) related program in fulfillment of requirements for admission to a subspecialty board examination which holds membership in the American Board of Medical Specialties. Upon completion of training and in order to maintain an affiliation with the College, the members are encouraged to apply to the Credentials Committee for status in one of the other three membership categories.

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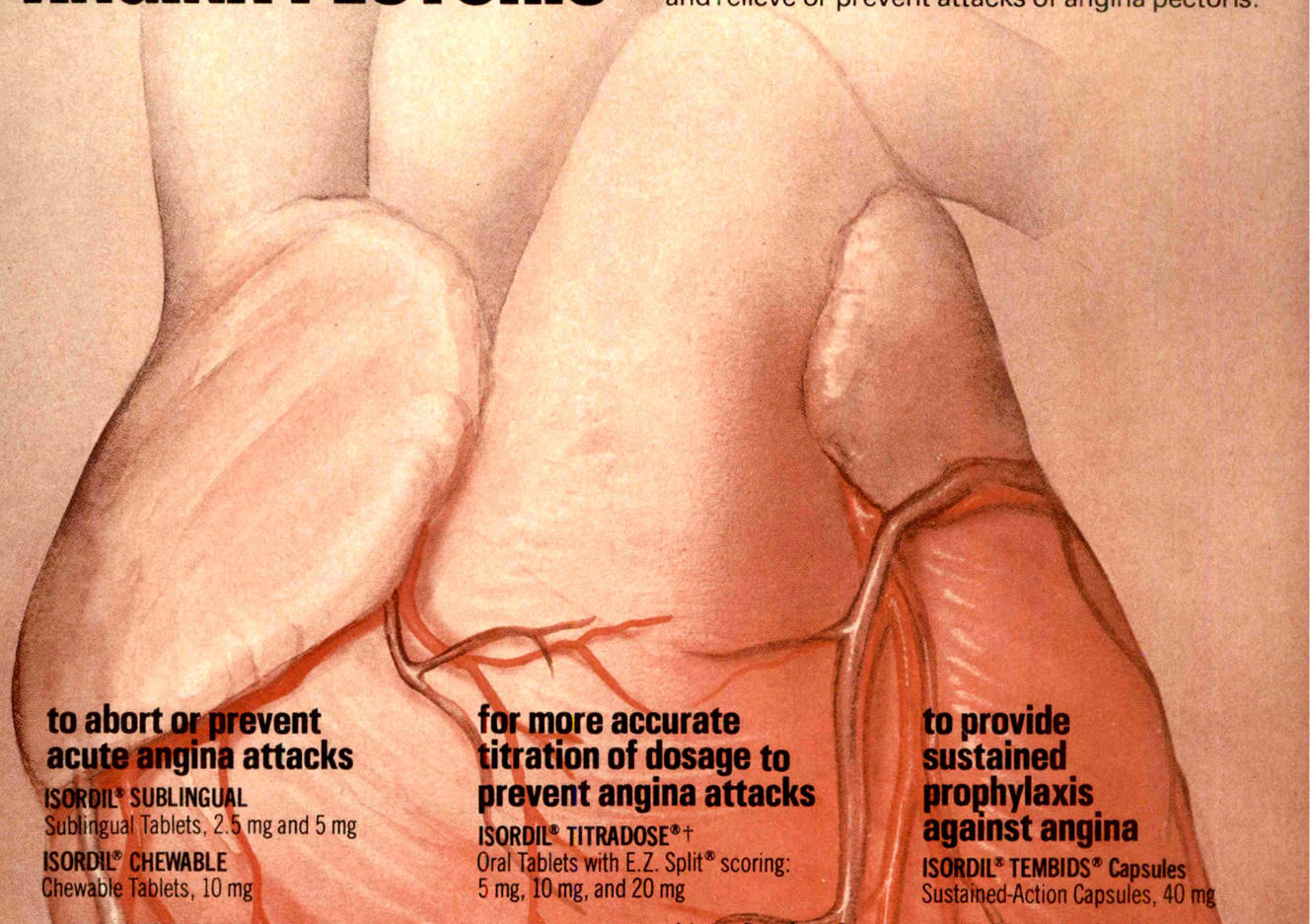

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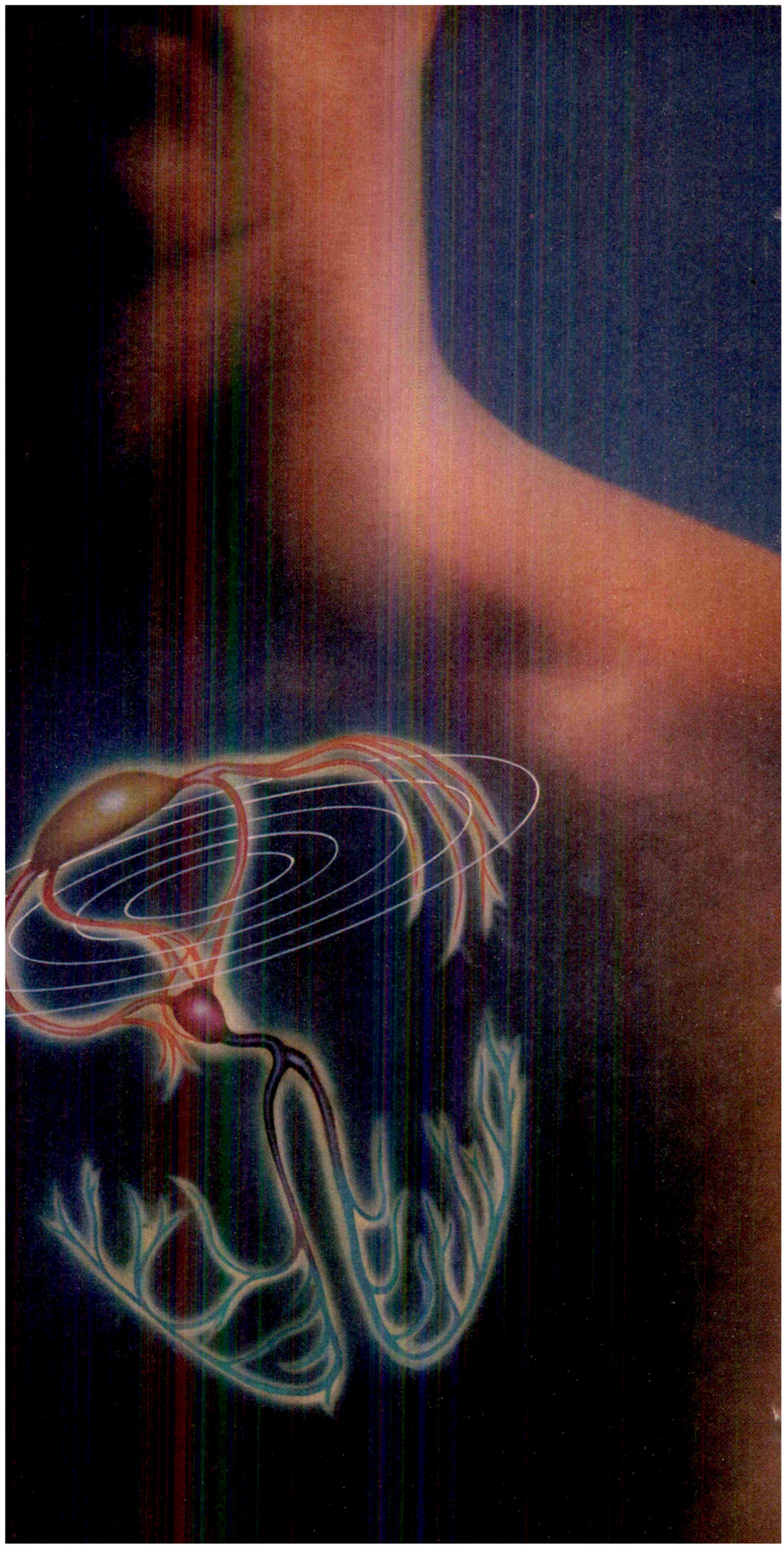

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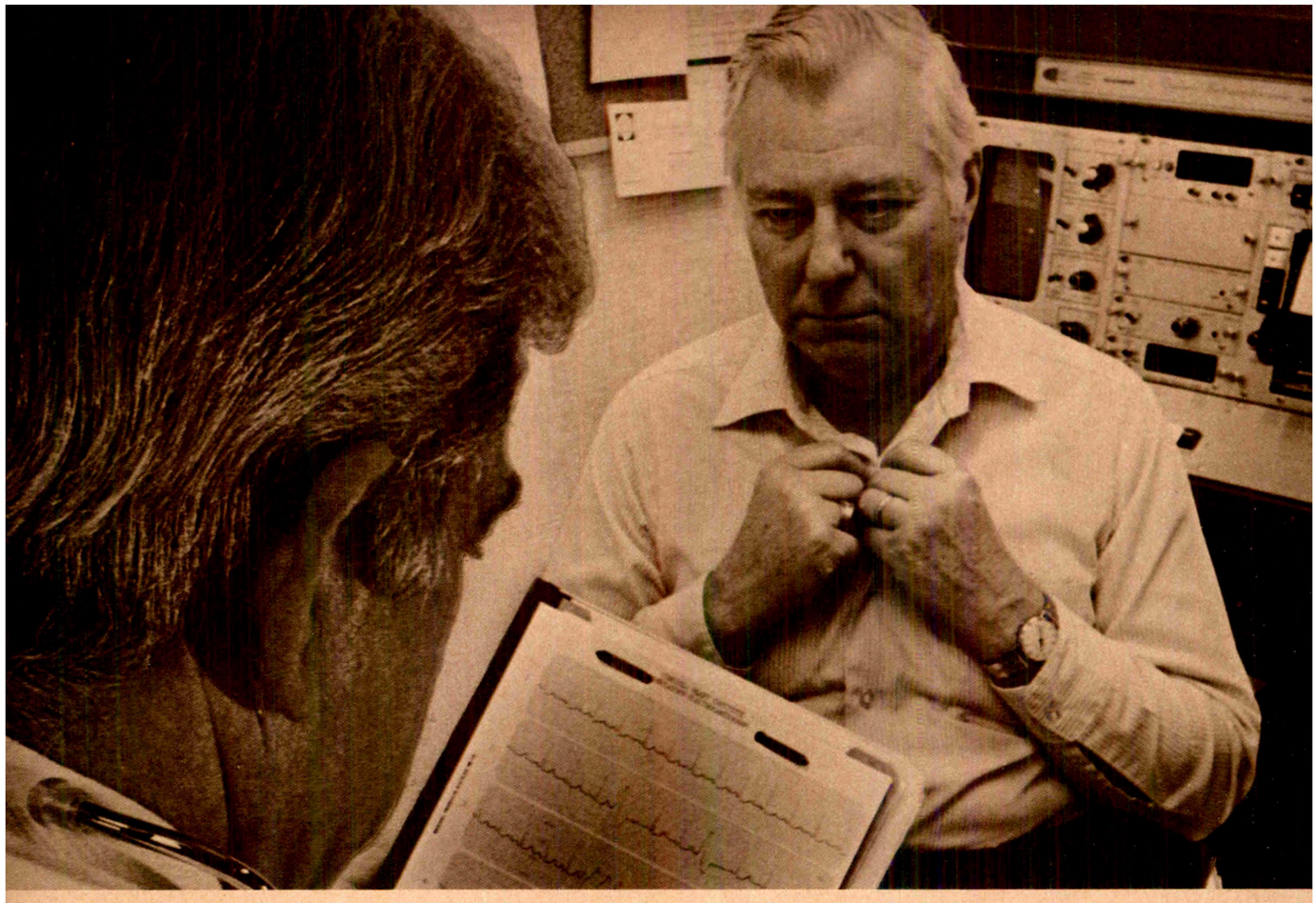

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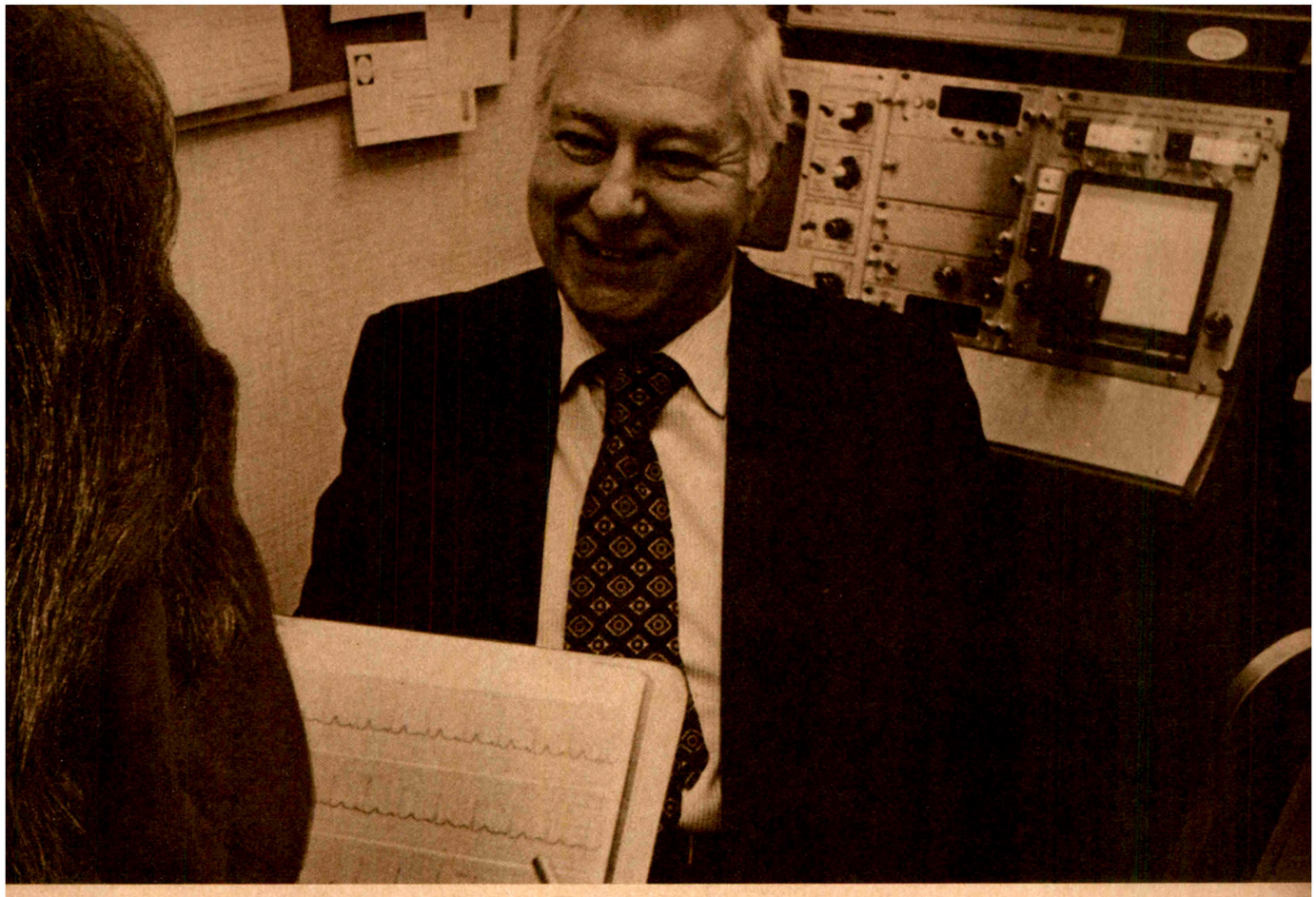
5 p.m.
9 p.m.



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300 mg in each Extentab

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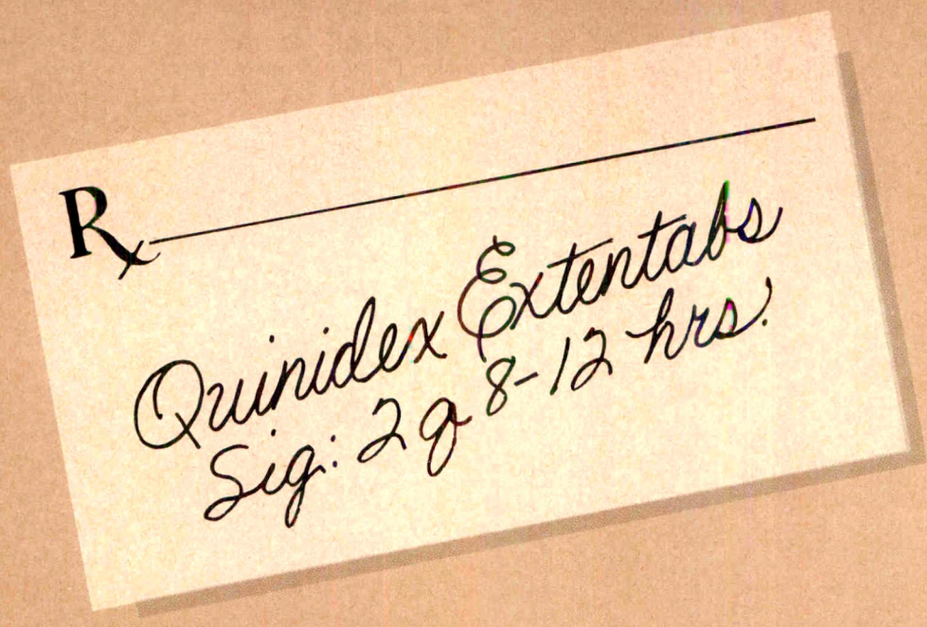

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Quinidex Extentabs are indicated in the treatment of:
Premature atrial and ventricular contractions.
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Paroxysmal A-V junctional rhythm.
Atrial flutter.
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Contraindications: Intraventricular conduction defects. A-V block. Idiosyncrasy or hypersensitivity.

Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.

Warning: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio and resulting extremely rapid ventricular rate.

Precautions: All the precautions applying to regular quinidine therapy apply to the Extentab form. Use with care in patients with severe congestive failure, renal insufficiency or with digitalis intoxication.

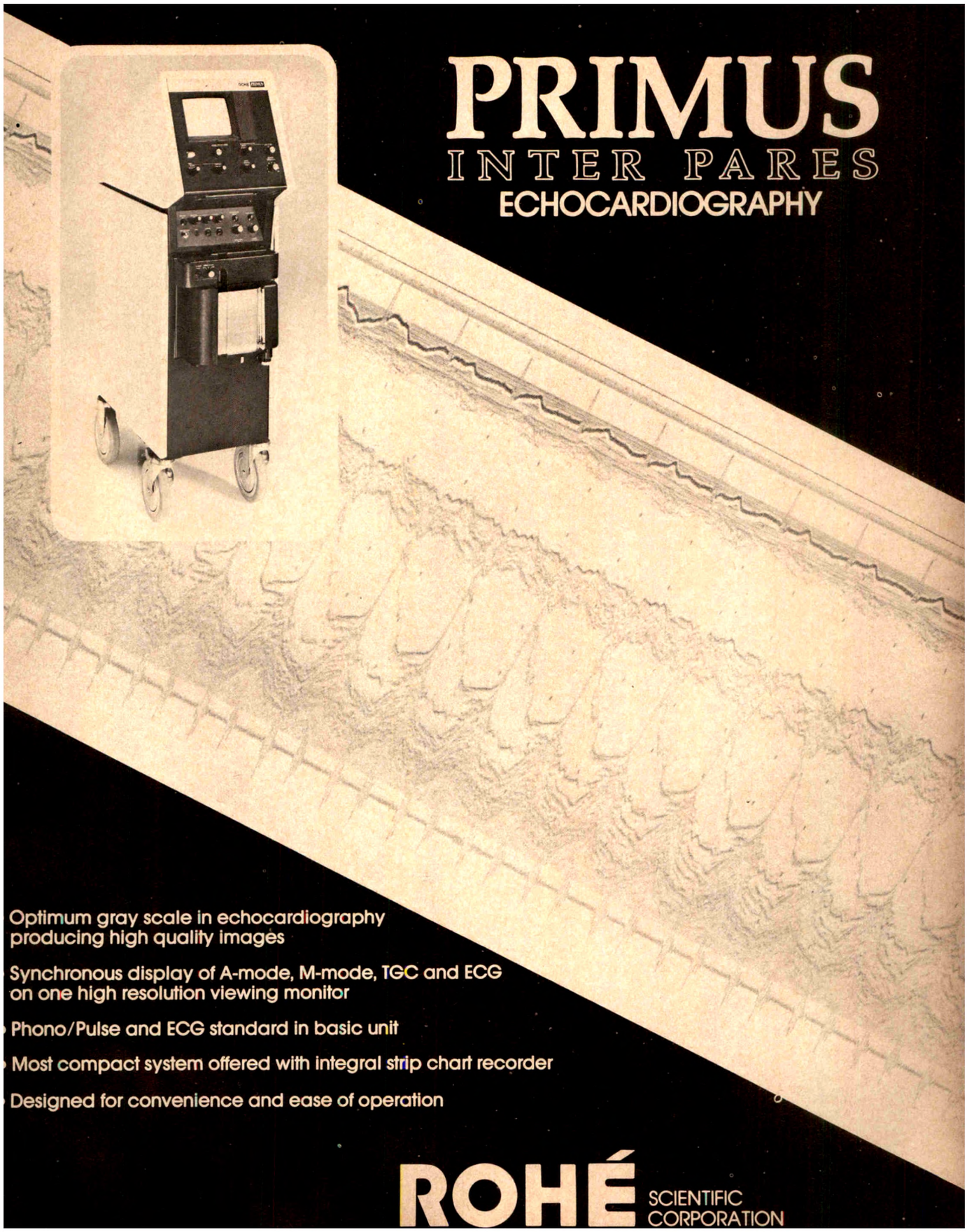
Patients should be carefully observed for signs of toxicity: e.g., (1) allergy or idiosyncrasy, such as febrile reactions, skin eruptions, and thrombocytopenia (extremely rare); (2) "cinchonism," such as tinnitus, blurred vision, dizziness, lightheadedness, and tremor; (3) G-I symptoms (nausea, vomiting, diarrhea, and colic); (4) cardiotoxic effects such as ventricular extrasystoles occurring at a rate of one or more every 6 normal beats, an increase of the QRS complex of 50% or more, a complete A-V block, or ventricular tachycardia.

NOTE: The development of "cinchonism" is not usually sufficient reason for terminating quinidine therapy. G-I symptoms can also be minimized by giving the drug with food.

Adverse Reactions: Cases of quinidine-induced hypoprothrombinemic hemorrhage in patients on chronic anticoagulant drug therapy have been reported.

Dosage: Two Quinidex Extentabs every 8 to 12 hours.

How Supplied: White sugar-coated Extentabs in bottles of 100 and 250 (NDC 0031-6649).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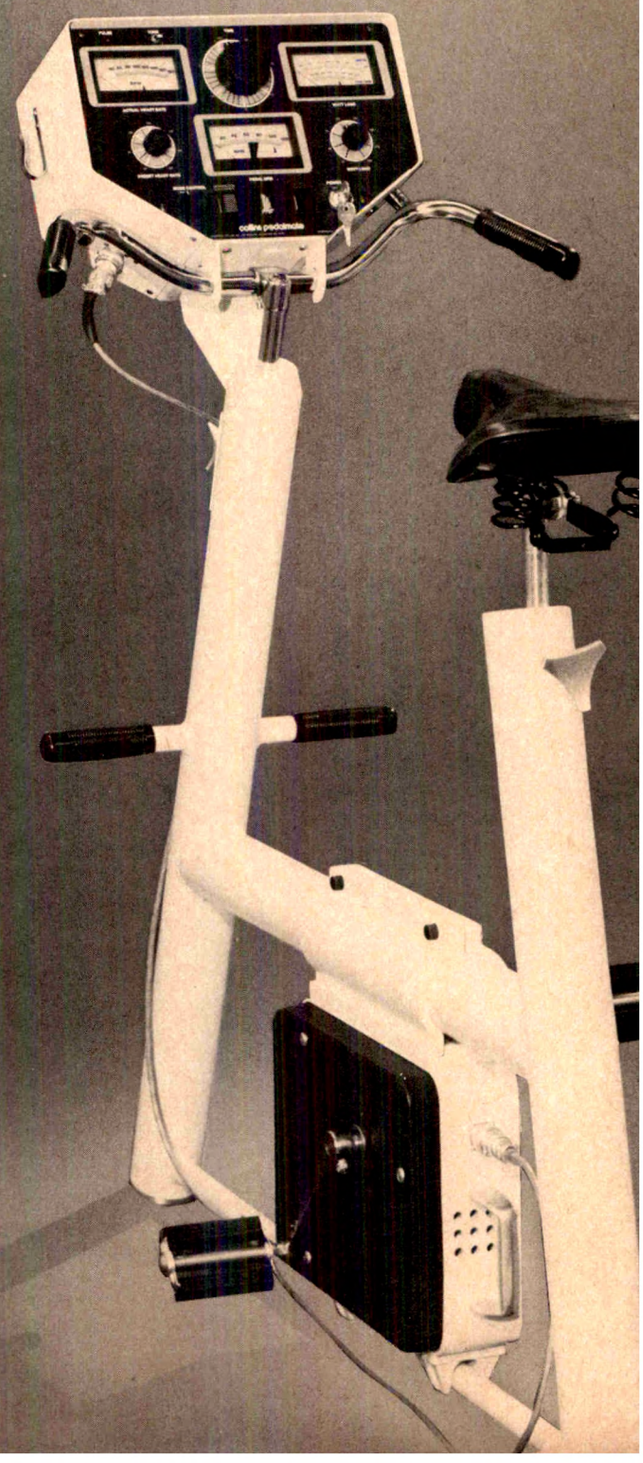

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When in the 'Manual Mode,' the Pedalmate presents the subject a constant load (manually variable) which remains constant independent of pedal rate.

SPECIFICATIONS

Heart Rate Control Accuracy:	±5 BPM
Heart Rate Accuracy:	±2% of reading
Watt Load Accuracy:	±5% of reading
Pedal Rate Accuracy:	±2% of reading (0-120 rpm)
Heart Rate Range:	40 to 180 BPM
Watt Load Range:	25 to 200 watts (150 to 1200 KPM/min.)
Pedal rpm Range:	0-120 rpm (30-120 rpm constant work)
Timer Range:	0 to 30 minutes
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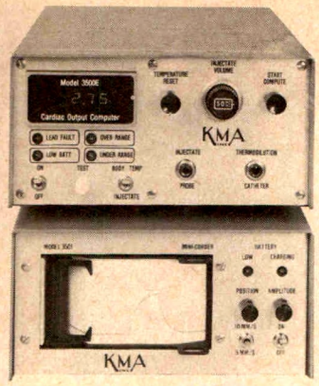

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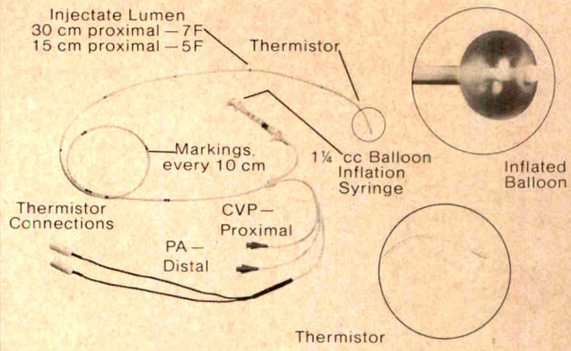

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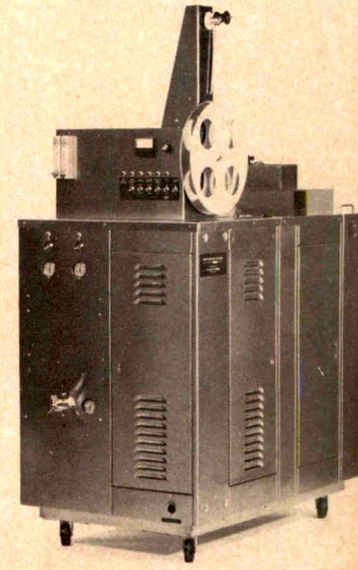

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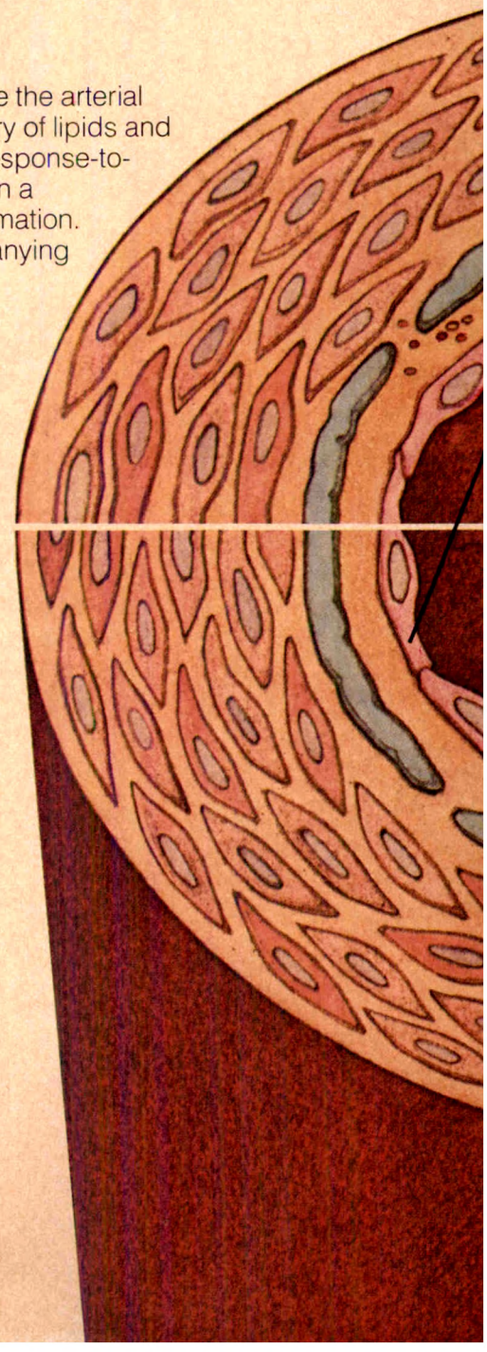
New Horizons in Hyperlipidemia

HIGH BLOOD PRESSURE & ELEVATED LIPIDS: PARTNERS IN PATHOLOGY

Hypertension and hyperlipidemia working in tandem can damage the arterial endothelium—the thin barrier that selectively prevents undue entry of lipids and other blood constituents into the arterial wall. According to the "response-to-injury" hypothesis,[1-3] a break in the endothelium is the first event in a pathologic sequence that can ultimately lead to arterial lesion formation. (See more detailed explanation of this hypothesis in the accompanying schematic illustration at right.)



Endothelial injury: a component of arterial response to hypertension

Animal and human studies[3,4] demonstrate that hypertension can injure the arterial endothelium. The damage seems to be related as much to local hemodynamic stresses at sites of vessel bending or branching[4,5] as to the height of the pressure. It has also been shown that the arterial intima is more permeable to plasma lipoproteins in hypertensive individuals than in normotensives.[6]

Chronic hyperlipidemia: a factor in initiating and maintaining lesions

In addition to causing lipid deposition in arterial plaques,[5] hyperlipidemia may be an initiating factor in lesion formation.[1] There is also evidence (from primate studies) that elevated serum lipid levels may inhibit the "normal" regression of arterial lesions following a single injury to the endothelium.[1]

1. Ross, R., and Harker, L.: Science *193*:1094 (Sept.) 1976.
2. Ross, R., and Glomset, J. A.: N. Engl. J. Med. *295*:420 (Aug. 19) 1976.
3. Schwartz, S. M.: Cardiovasc. Med. *2*:991 (Oct.) 1977.
4. Glagov, S.: Med. Clin. North Am. *57*:63 (Jan.) 1973.
5. DiGirolamo, M., and Schlant, R. C., in Hurst, J. W., *et al.* (eds.): The Heart, 4th ed., New York, McGraw-Hill, 1978, pp. 1114, 1116.
6. Smith, E. B., and Slater, R. S., in Atherogenesis: Initiating Factors, CIBA Foundation Symposium *12*:39, 1973.

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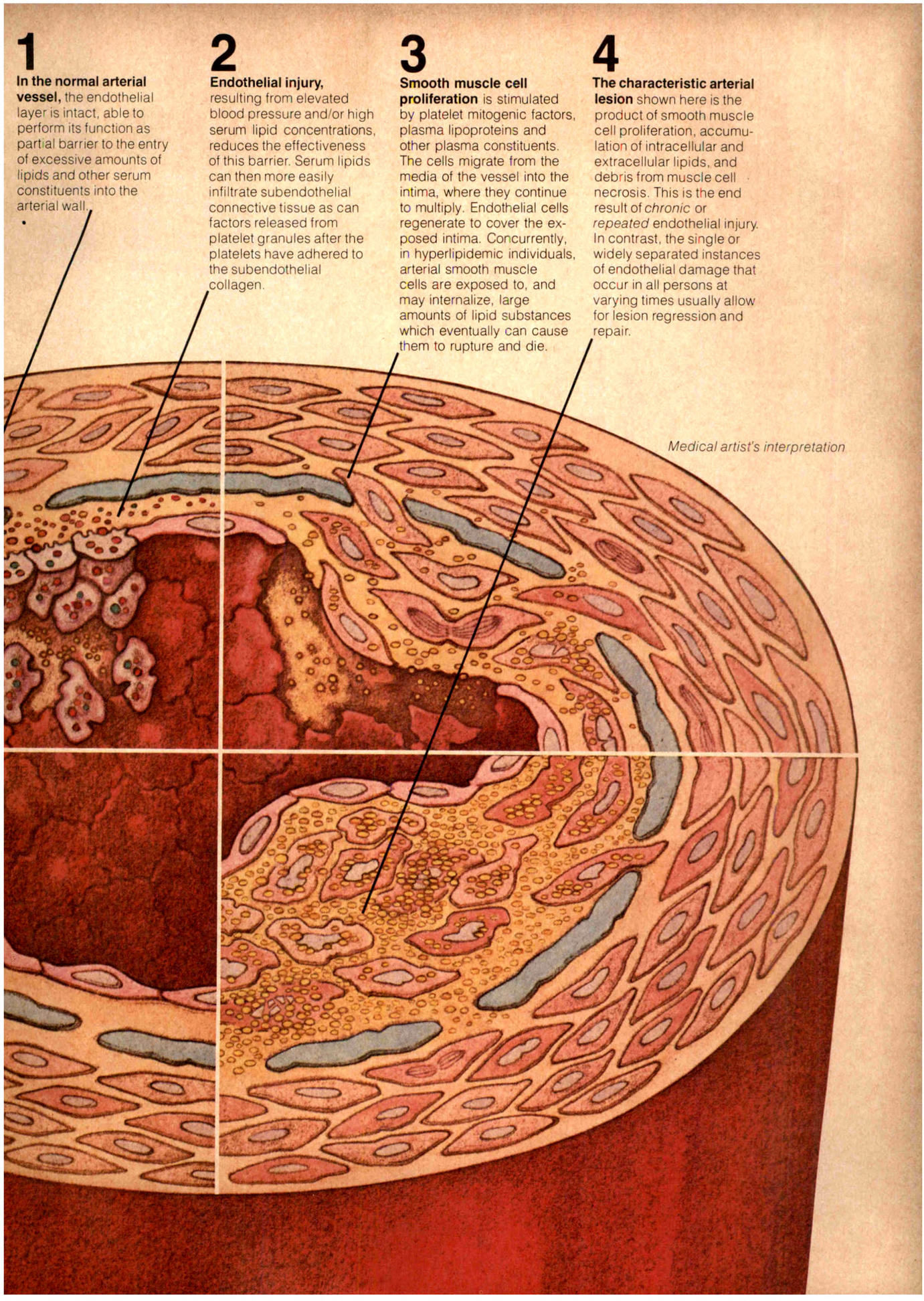
1
In the normal arterial vessel, the endothelial layer is intact, able to perform its function as partial barrier to the entry of excessive amounts of lipids and other serum constituents into the arterial wall.
2
Endothelial injury, resulting from elevated blood pressure and/or high serum lipid concentrations, reduces the effectiveness of this barrier. Serum lipids can then more easily infiltrate subendothelial connective tissue as can factors released from platelet granules after the platelets have adhered to the subendothelial collagen.
3
Smooth muscle cell proliferation is stimulated by platelet mitogenic factors, plasma lipoproteins and other plasma constituents. The cells migrate from the media of the vessel into the intima, where they continue to multiply. Endothelial cells regenerate to cover the exposed intima. Concurrently, in hyperlipidemic individuals, arterial smooth muscle cells are exposed to, and may internalize, large amounts of lipid substances which eventually can cause them to rupture and die.
4
The characteristic arterial lesion shown here is the product of smooth muscle cell proliferation, accumulation of intracellular and extracellular lipids, and debris from muscle cell necrosis. This is the end result of chronic or repeated endothelial injury. In contrast, the single or widely separated instances of endothelial damage that occur in all persons at varying times usually allow for lesion regression and repair.
Medical artist's interpretation

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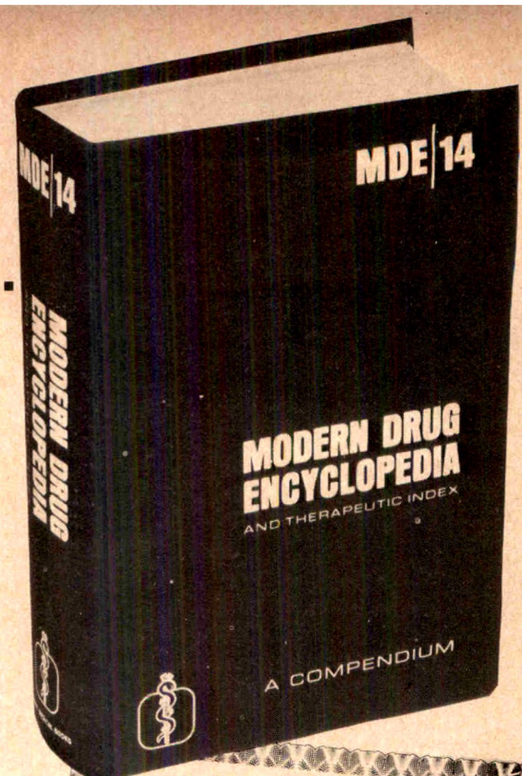

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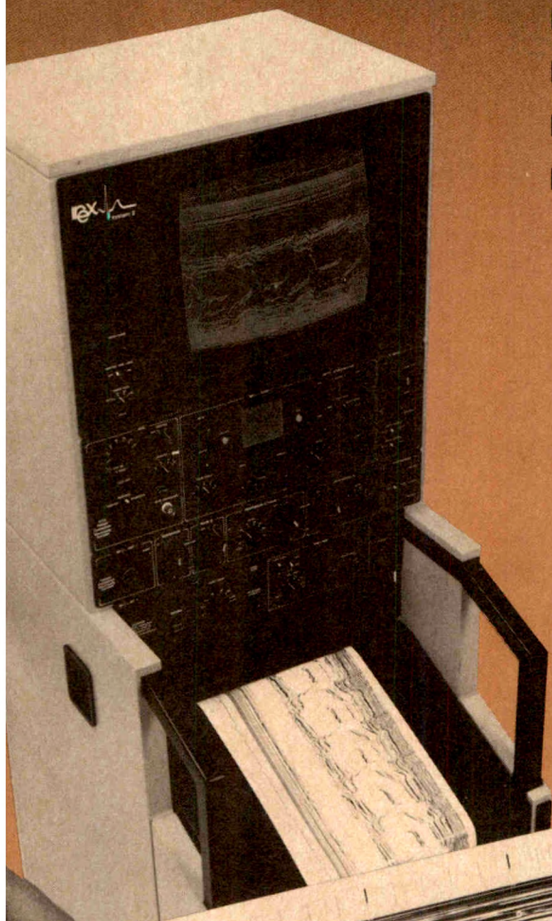

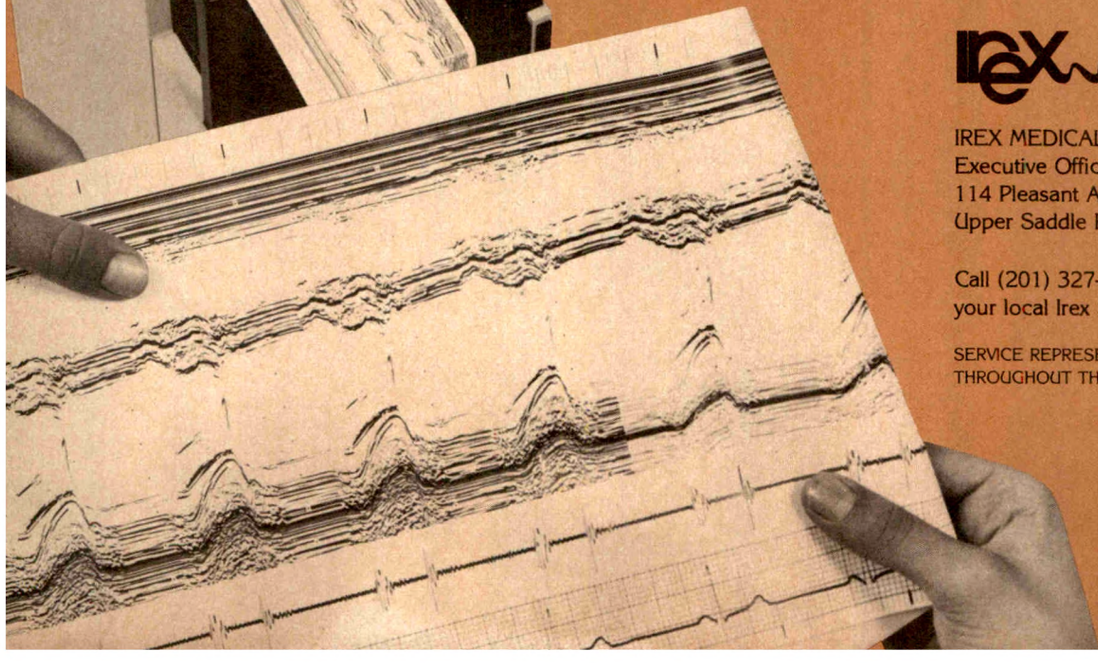

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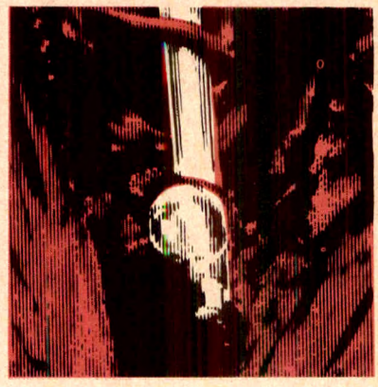

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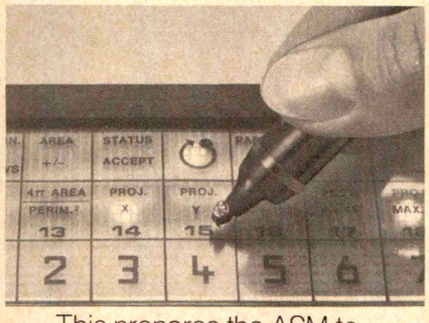

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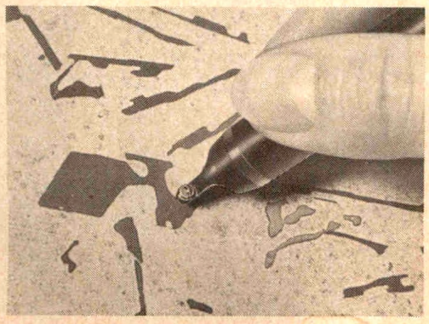

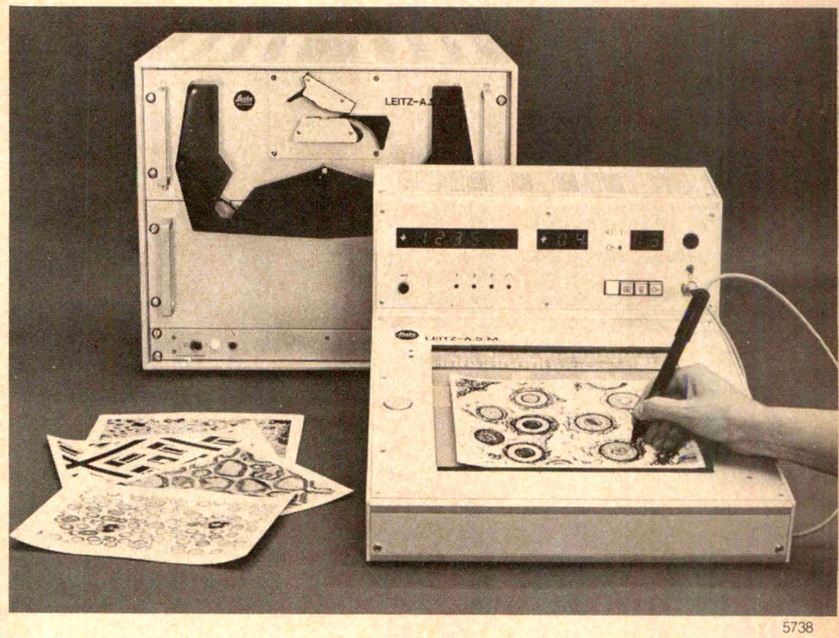

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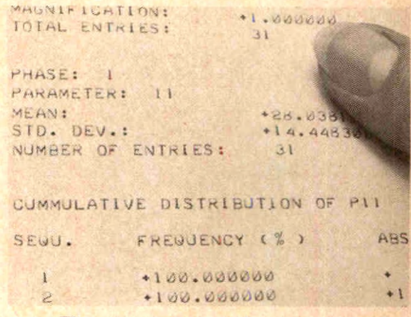

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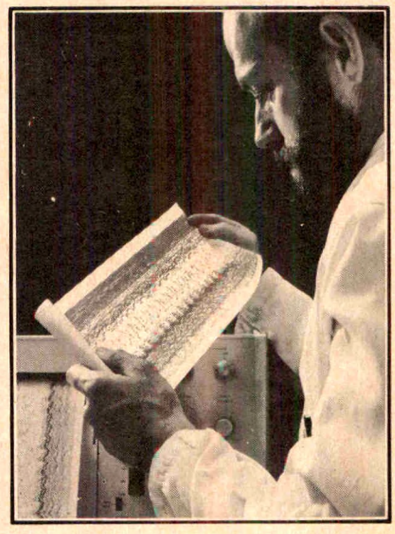

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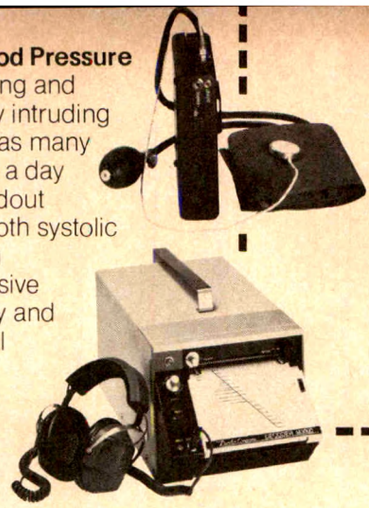

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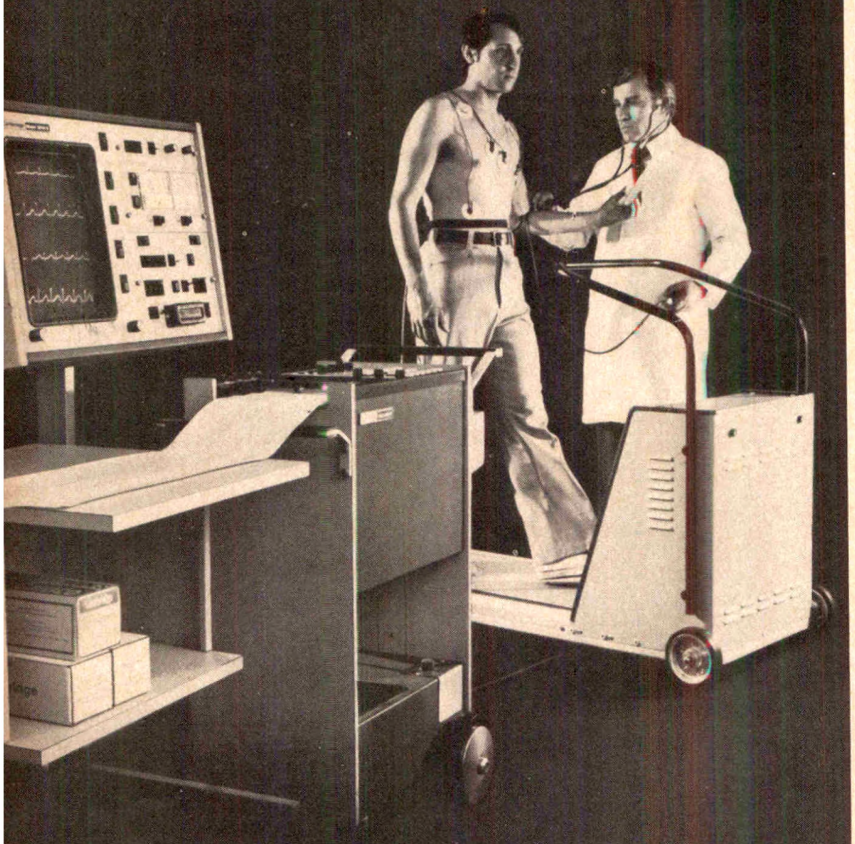

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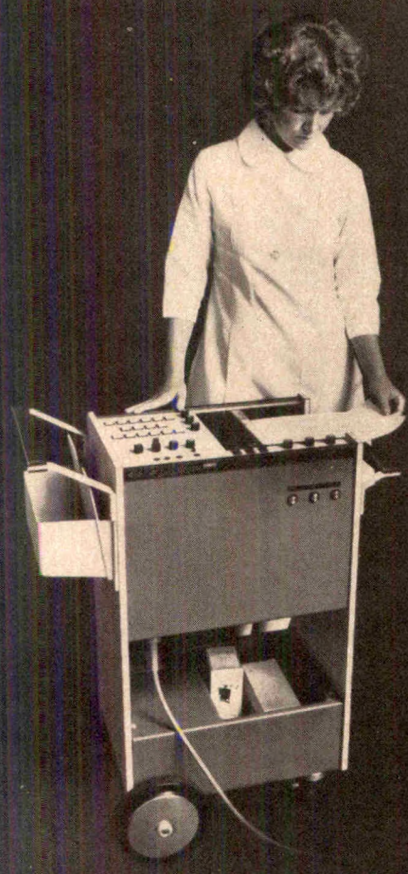

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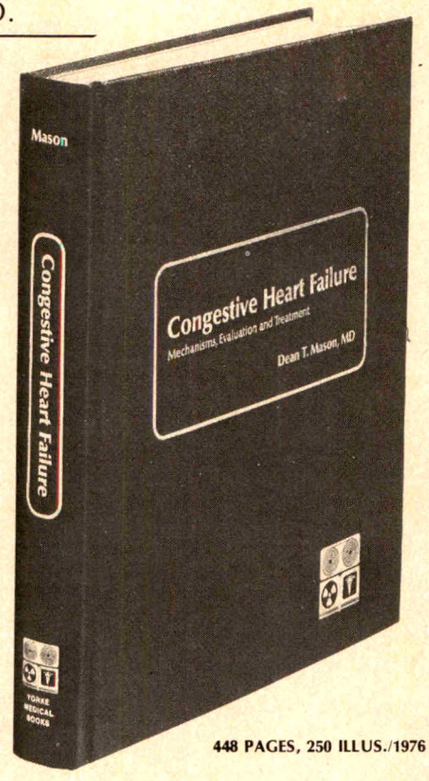

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About the author . . . Dean T. Mason, M.D.

Professor of Medicine, Professor Physiology, Chief of Cardiovascular Medicine, University of California, School of Medicine, Davis

President, American College of Cardiology President, Western Society for Clinical Research

Member of the American Board of Internal Medicine Cardiovascular Diseases

Has authored more than 400 original articles on cardiovascular science and clinical cardiology.

Serves on the editorial boards of The American Journal of Cardiology, The Journal of Clinical Investigation, Circulation, Chest, Clinical Pharmacology and Therapeutics, Catheterization and Cardiovascular Diagnosis, and Heart and Lung.

Recipient of Experimental Therapeutics Award in 1973 from the American Society of Pharmacology and Experimental Therapeutics, the Research Awards in 1965 from the American Therapeutic Society, and the Theodore and Susan B. Cummings Humanitarian Awards in 1972, 1973, and 1975 from the U.S. State Department and the American College of Cardiology.

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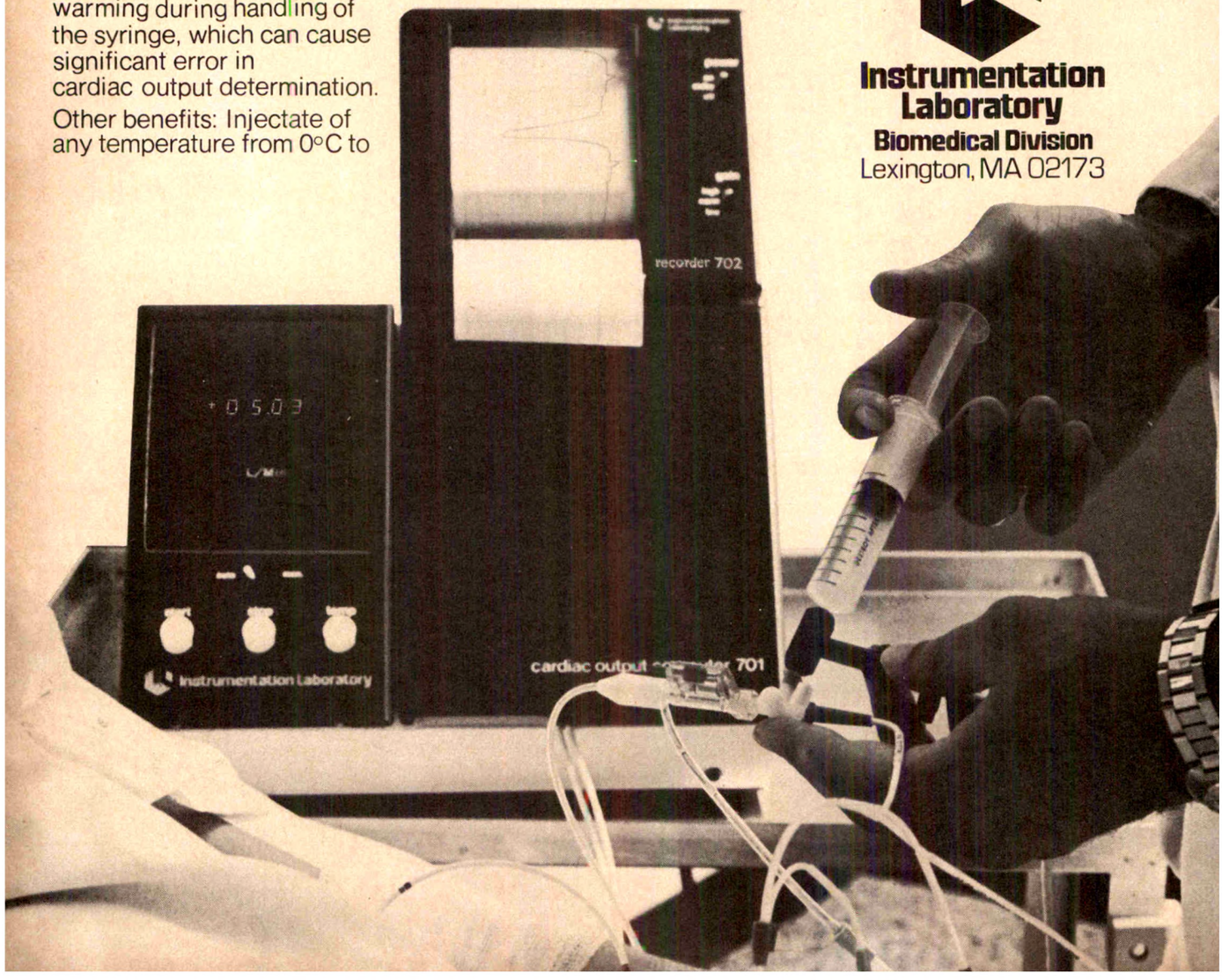

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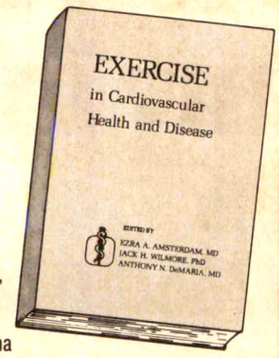

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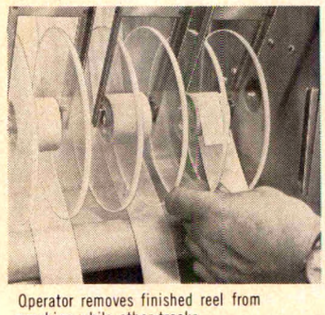

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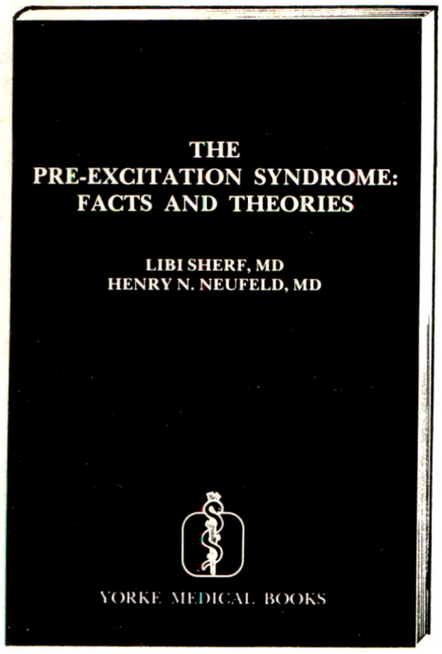

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Libi Sherf, MD, FACC
Henry N. Neufeld, MD, FACC
Heart Institute, Chaim Sheba Medical Center, University of Tel Aviv, Sackler School of Medicine

For September 1978 publication

288 pages, 110 illus., 1,000 ref.
$33.00

Every Cardiologist, Internist, Pediatrician, Surgeon — Indeed, *Every Physician* — Should Have a Good Basic Knowledge of The Pre-excitation Syndrome. Here Are Just a Few Reasons Why This is so Essential:

- ☐ ⅓ of all pre-excitation cases are misdiagnosed.
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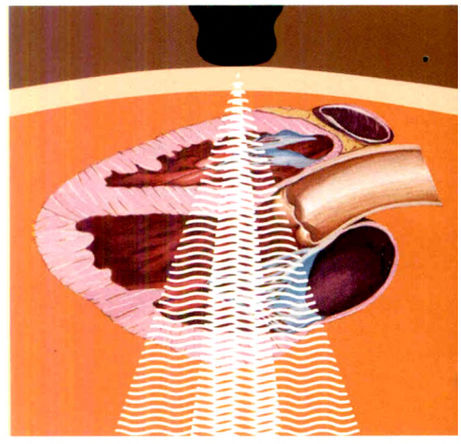

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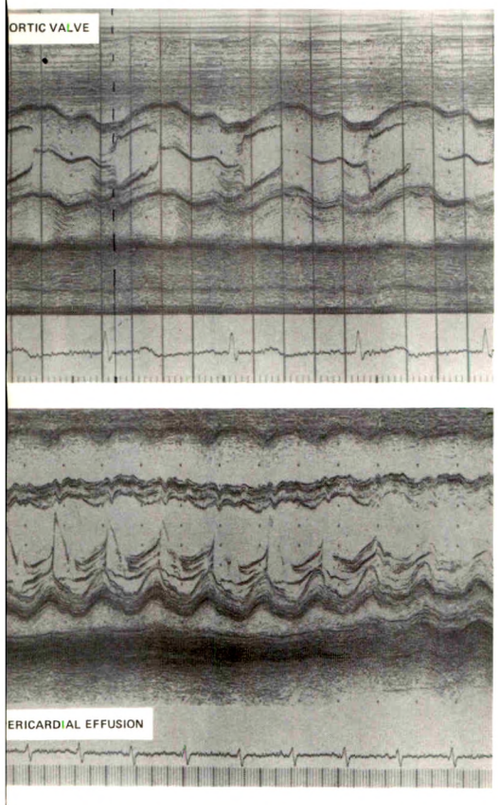

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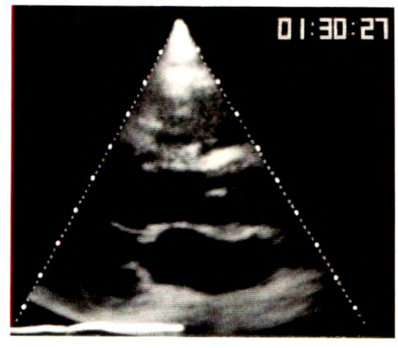

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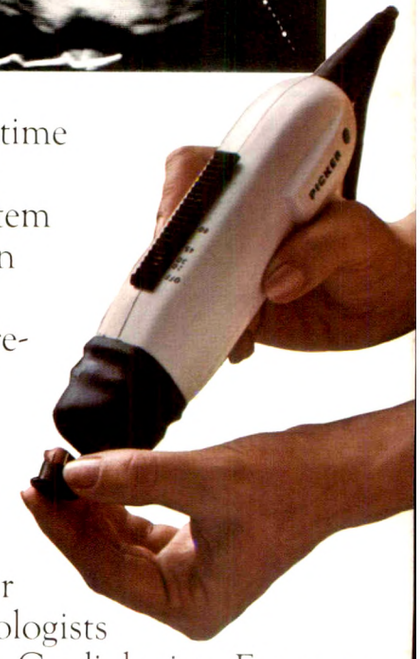

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Aldactazide®

(spironolactone 25 mg./
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WARNING

Spironolactone, an ingredient of Aldactazide, has been shown to be a tumorigen in chronic toxicity studies in rats (see *Warnings*). Aldactazide should be used only in those conditions described under *Indications*. Unnecessary use of this drug should be avoided.

Fixed-dose combination drugs are not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Indications: Cirrhosis of the liver accompanied by edema and/or ascites. Essential hypertension, edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate.

Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, hyperkalemia or acute or severe hepatic failure. Allergy to thiazide diuretics or to other sulfonamide-derived drugs.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactazide. Do not administer concurrently with other potassium-sparing diuretics. Sulfonamide derivatives including thiazides have been reported to exacerbate or activate systemic lupus erythematosus.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75 and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hypokalemia may develop as a result of profound diuresis, particularly when Aldactazide is used concomitantly with loop diuretics, glucocorticoids or ACTH. Transient elevation of BUN may occur. Dilutional hyponatremia or rarely low-salt syndrome may develop. Gynecomastia may develop and in rare instances some breast enlargement may persist.

Thiazides may alter the metabolism of uric acid and carbohydrates with possible hyperuricemia, gout and decreased glucose tolerance. Vascular responsiveness to norepinephrine is reduced. Thiazides may also increase the responsiveness to tubocurarine. Thiazides may decrease serum PBI levels and prolonged therapy may induce hypercalcemia and hypophosphatemia.

Spironolactone may and hydrochlorothiazide does cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. Breast feeding should be discontinued when Aldactazide is being used.

Adverse Reactions:

Associated with spironolactone: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established.

Associated with thiazides: Gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhea, abdominal cramps), purpura, thrombocytopenia, leukopenia, agranulocytosis, dermatologic symptoms (cutaneous eruptions, pruritus, erythema multiforme), paresthesia, acute pancreatitis, jaundice, dizziness, vertigo, headache, xanthopsia, photosensitivity, necrotizing angiitis, aplastic anemia, orthostatic hypotension, muscle spasm, weakness and restlessness.

Adverse reactions are usually reversible upon discontinuation of Aldactazide.

Dosage and Administration

Edema in adults: The usual maintenance dose is one tablet four times daily but may range from one to eight tablets daily depending on the response to the initial titration.

Edema in children: The usual daily maintenance dose should be that which provides 0.75 to 1.5 mg. of spironolactone per pound of body weight (1.65 to 3.3 mg./kg.).

Essential hypertension: Usually two to four tablets daily depending on results of the titration of the individual ingredients.

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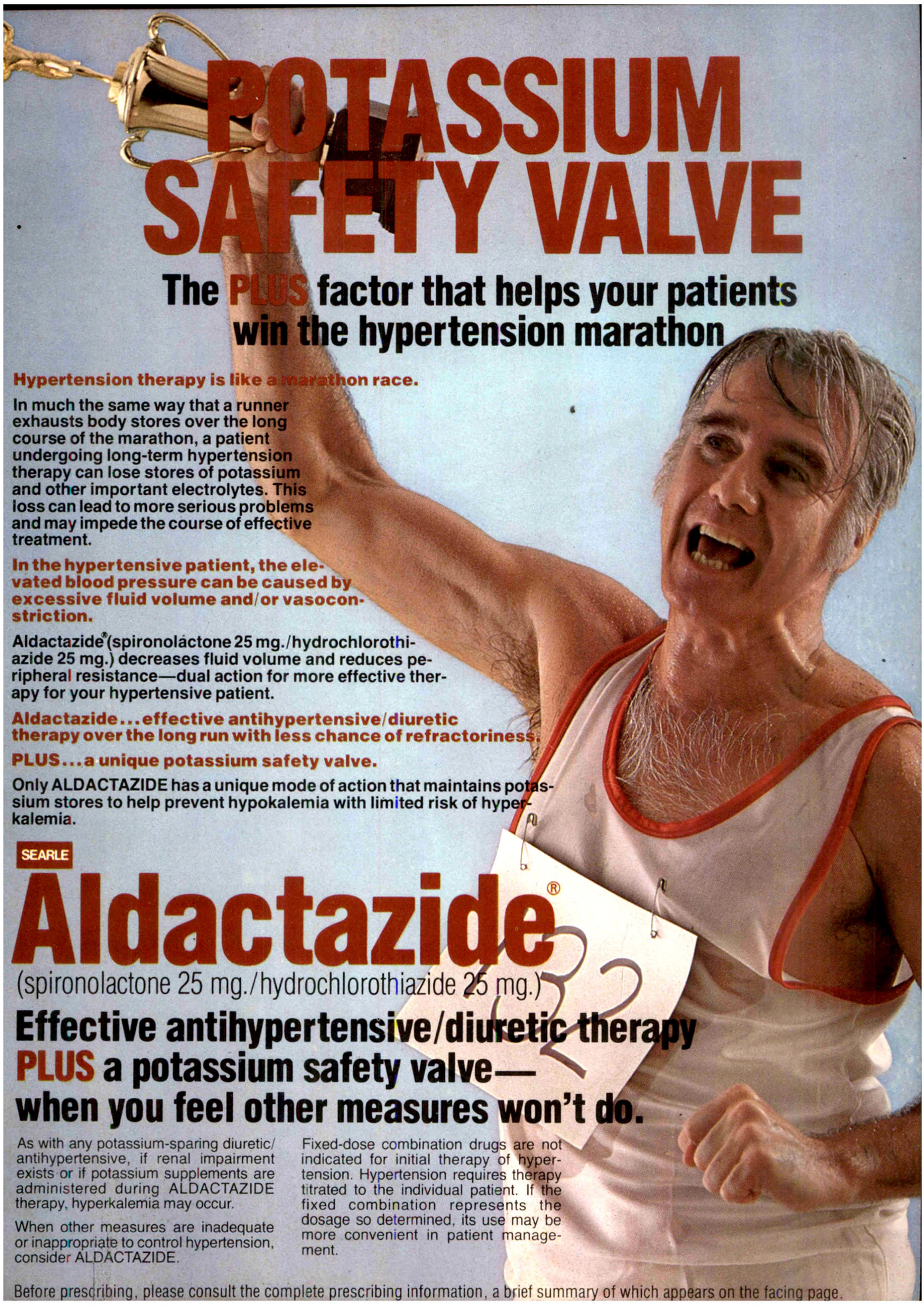

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As with any potassium-sparing diuretic/antihypertensive, if renal impairment exists or if potassium supplements are administered during ALDACTAZIDE therapy, hyperkalemia may occur.

When other measures are inadequate or inappropriate to control hypertension, consider ALDACTAZIDE.

Fixed-dose combination drugs are not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management.

Before prescribing, please consult the complete prescribing information, a brief summary of which appears on the facing page.

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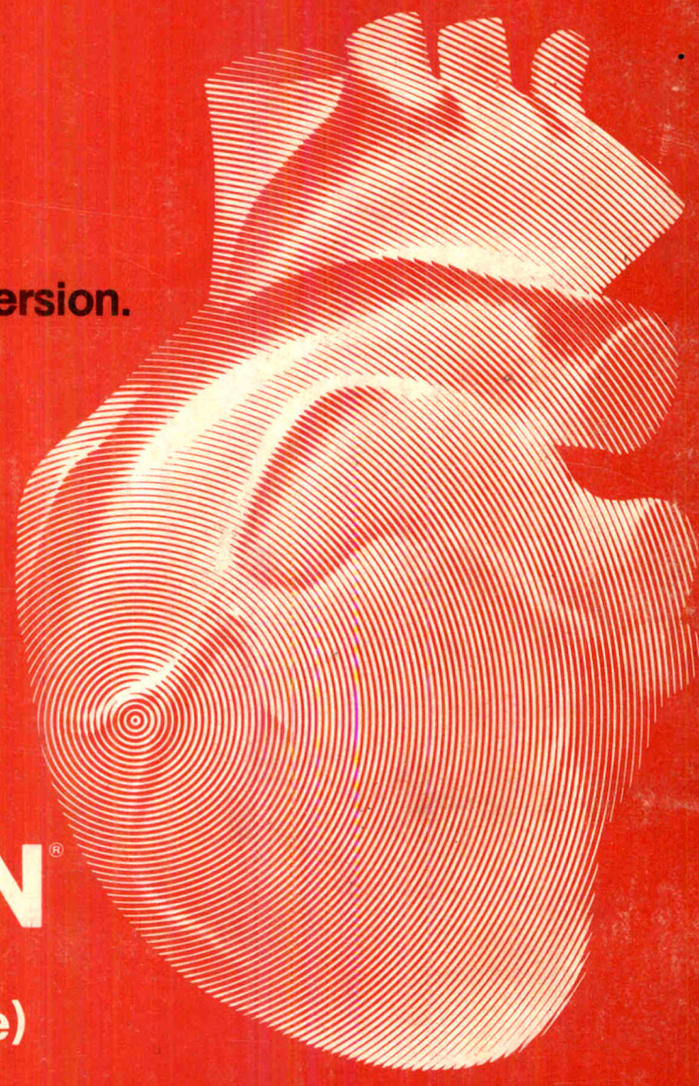

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*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 50.

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20/20

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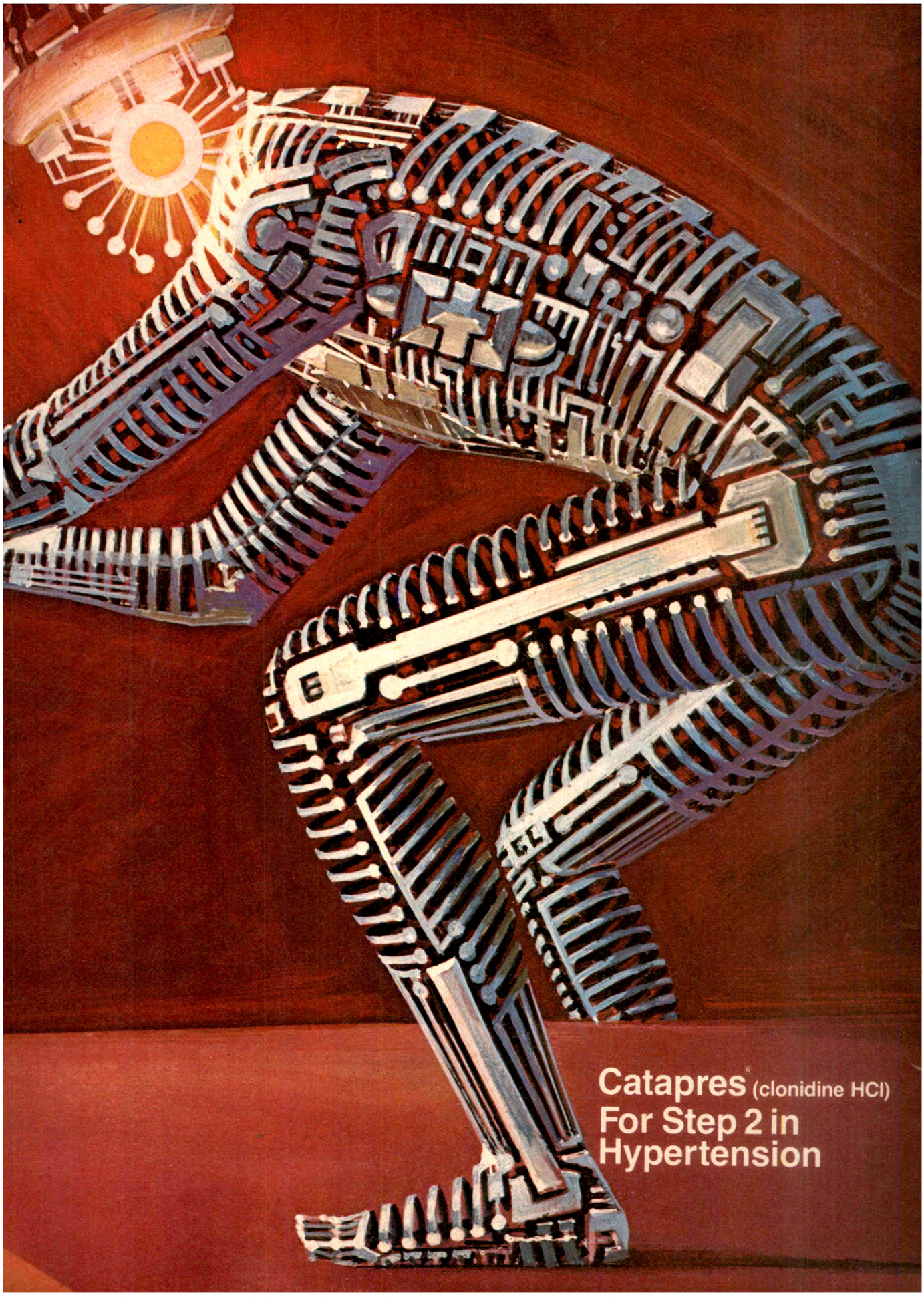
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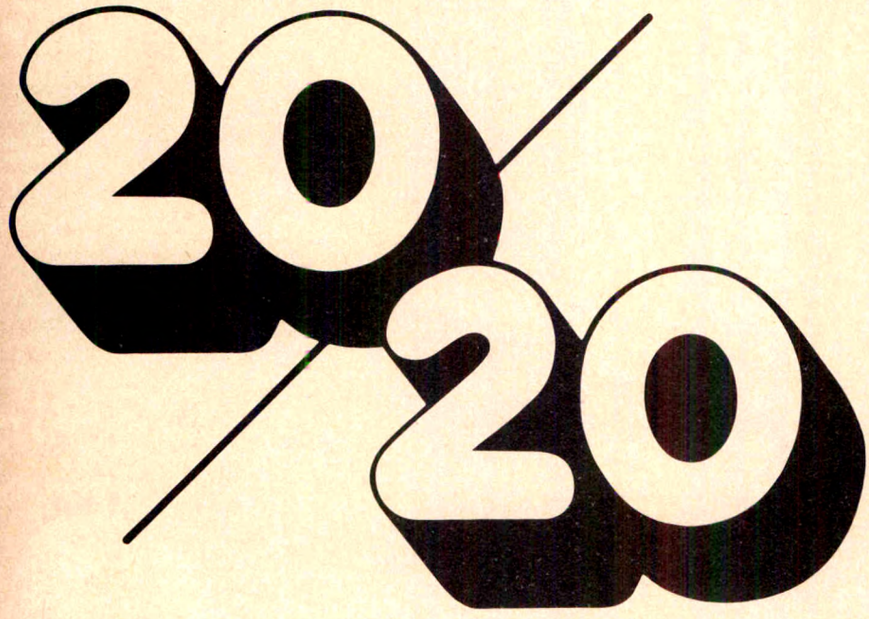

What you do the first 20 days Can help him the next 20 years

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Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in poter It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fet
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressur and associated subjective symptoms such as nervous ness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulti their physician. Rare instances of hypertensive encep lopathy and death have been recorded after cessatior of clonidine hydrochloride therapy. A causal relation- ship has not been established in these cases. It has been demonstrated that an excessive rise in blood pr sure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intrave- nous phentolamine. Patients who engage in poten- tially hazardous activities, such as operating machine or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects o alcohol, barbiturates and other sedatives. Like any ot agent lowering blood pressure, clonidine hydrochlori should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochlori should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorde with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increas in the incidence and severity of spontaneously occur ring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported Generally these effects tend to diminish with continu therapy. The following reactions have been associate with the drug, some of them rarely. (In some instance an exact causal relationship has not been establishe These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver fun tion tests; one report of possible drug-induced hepa- titis without icterus and hyperbilirubinemia in a patie receiving clonidine hydrochloride, chlorthalidone, an papaverine hydrochloride. Weight gain, transient ele tion of blood glucose, or serum creatine phosphokina congestive heart failure, Raynaud's phenomenon; viv dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mer depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of t eyes, dryness of the nasal mucosa, pallor, gyneco- mastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somn lence, diminished or absent reflexes and vomiting fol lowed the accidental ingestion of Catapres (clonidin hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of a analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all ef- fects of Catapres (clonidine hydrochloride) overdosag

How Supplied: Catapres, brand of clonidine hydro- chloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000.

For complete details, please see full prescribing information.

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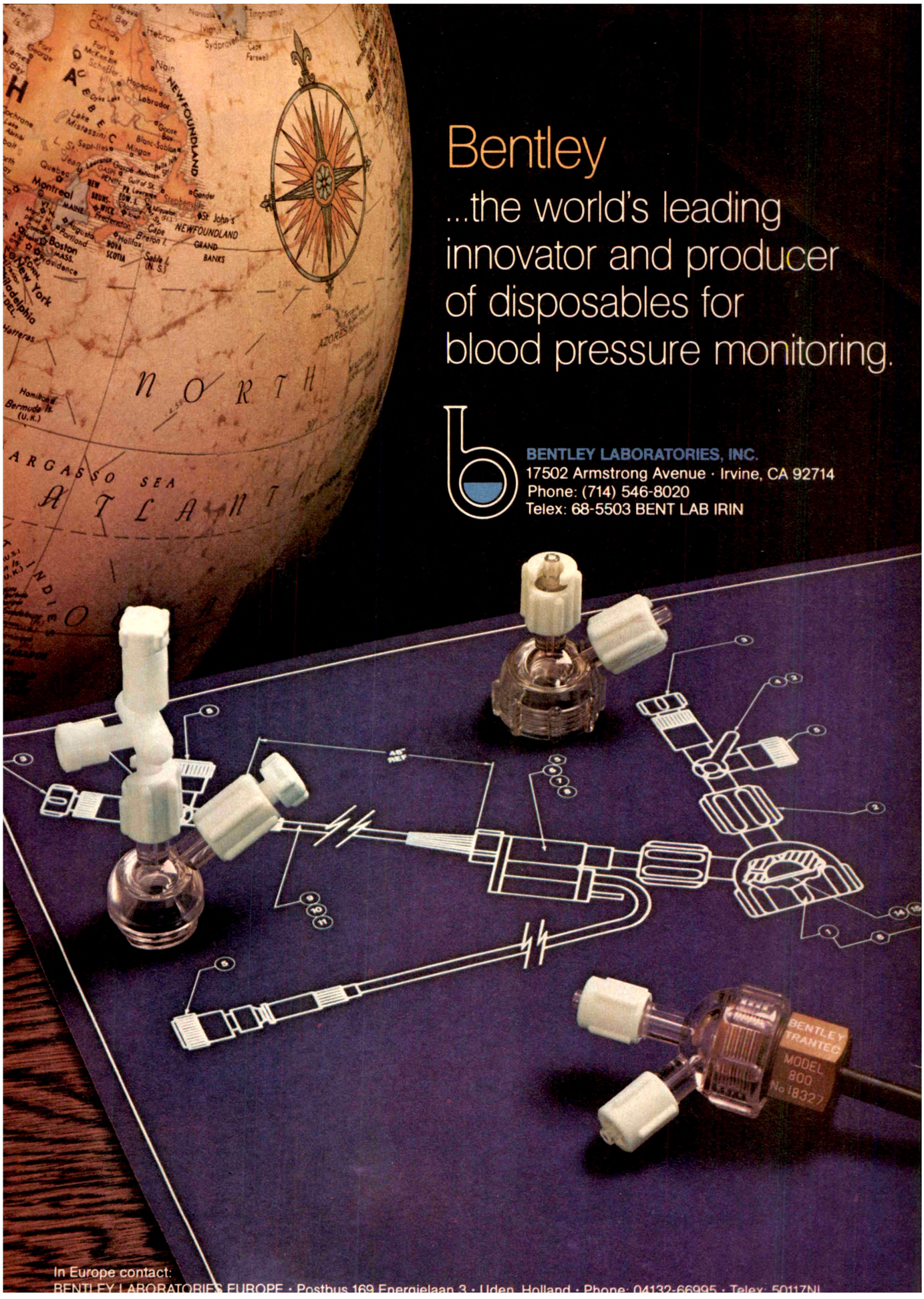
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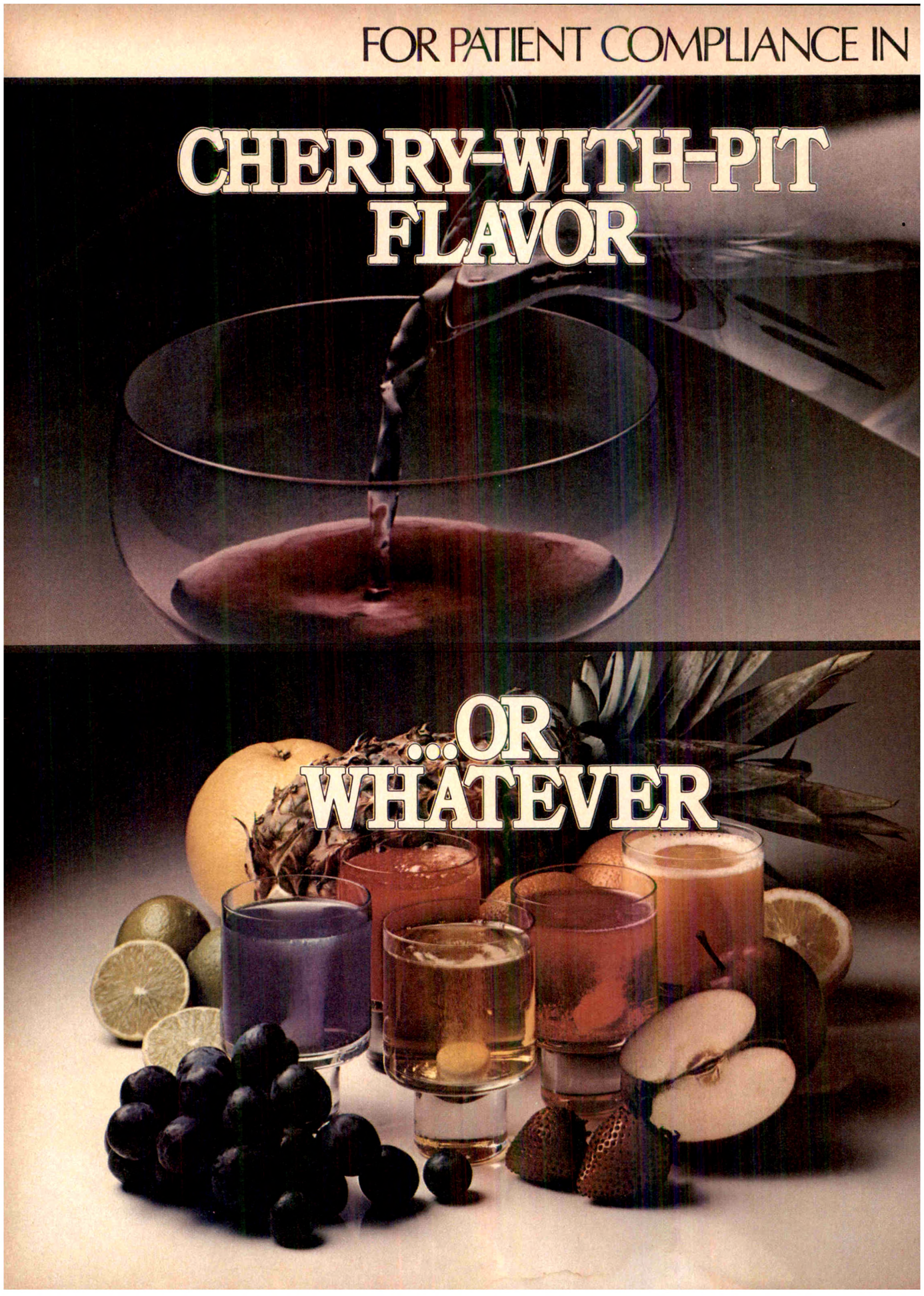

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Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

Indications: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

Contraindications: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements.

Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis.

High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest.

To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve each Klorvess Effervescent Tablet in 3 to 4 ounces of water or fruit juice, or dilute each tablespoonful of Klorvess (potassium chloride) 10% Liquid in 3 to 4 ounces of water. Both of these solutions should be ingested slowly with or immediately after meals.

Adverse Reactions: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts.

The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest.

The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

Dosage and Administration: Klorvess Effervescent Tablets: Adults—One Klorvess Effervescent Tablet (20 mEq each of potassium and chloride) completely dissolved in 3 to 4 ounces of cold water or fruit juice 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) of Klorvess Liquid (20 mEq of potassium chloride) completely diluted in 3 to 4 ounces of water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating. Deviations from these recommended dosages may be indicated in certain cases of hypokalemia based upon the patient's status. The average total daily dosage must be governed by the patient's response as determined by frequent evaluation of serum electrolytes, EKG and clinical status.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

Treatment of Hyperkalemia: 1. Dextrose solution, 10 or 25% containing 10 units of crystalline insulin per 20 g dextrose, given IV in a dose of 300 to 500 ml in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resins, orally and as retention enema. (Caution: Ammonium compounds should not be used in patients with hepatic cirrhosis.) 3. Hemodialysis and peritoneal dialysis. 4. The use of potassium-containing foods or medicaments must be eliminated. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

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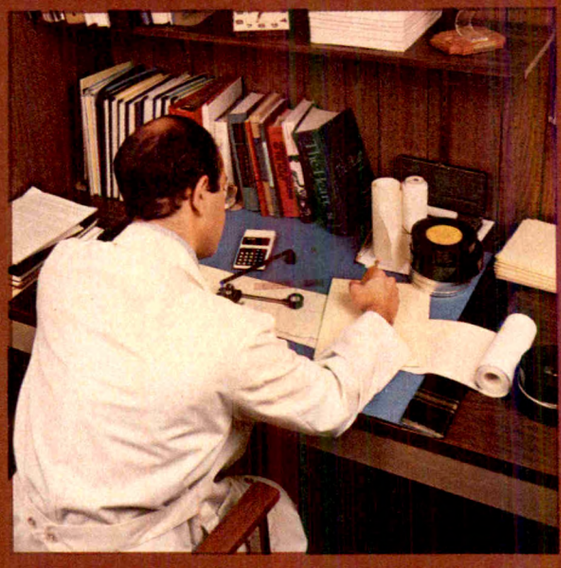

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CLINICAL STUDIES

345 **Myocardial Imaging With Thallium-201: A Multicenter Study in Patients With Angina Pectoris or Acute Myocardial Infarction**

JAMES L. RITCHIE, BARRY L. ZARET, H. WILLIAM STRAUSS, BERTRAM PITT, DANIEL S. BERMAN, HEINRICH R. SCHELBERT, WILLIAM L. ASHBURN, HARVEY J. BERGER and GLEN W. HAMILTON

This multicenter cooperative study of 190 patients employing rest and exercise thallium-201 myocardial imaging found that smaller infarctions, as assessed with serum enzyme values, and diaphragmatic infarctions were less commonly detected than larger or anterior infarctions. These results suggest that myocardial imaging complements the electrocardiographic identification of acute myocardial infarction or exercise-induced myocardial ischemia. The diagnostic sensitivity of rest/exercise thallium-201 imaging, when combined with rest/exercise electrocardiography, was greater than that achieved with either study alone. This combination detected coronary disease in 91 percent of all patients with angiographically documented coronary artery disease.

351 **Exercise-Induced Left Ventricular Dysfunction in Symptomatic and Asymptomatic Patients With Aortic Regurgitation: Assessment With Radionuclide Cineangiography**

JEFFREY S. BORER, STEPHEN L. BACHARACH, MICHAEL V. GREEN, KENNETH M. KENT, WALTER L. HENRY, DOUGLAS R. ROSING, STUART F. SEIDES, GERALD S. JOHNSTON and STEPHEN E. EPSTEIN. *With the technical assistance of* BONNIE MACK

Left ventricular ejection fraction determined with noninvasive radionuclide cineangiography increased with exercise in 30 normal subjects. In patients with severe aortic regurgitation the ejection fraction was normal at rest in 14 of 21 symptomatic patients but normal during exercise in only 1. Ejection fraction was normal at rest in 21 of 22 asymptomatic patients but was normal during exercise in only 13. Exercise-induced left ventricular dysfunction can precede symptoms and dysfunction at rest. Such serial assessment may prove useful in following the degree of left ventricular function in patients before the onset of symptoms or of irreversible left ventricular failure. Such subnormal ejection fractions during exercise generally appear before the manifestations of left ventricular dysfunction commonly assessed noninvasively or at cardiac catheterization.

358 **Prevalence of Right Ventricular Involvement in Inferior Wall Infarction Assessed With Myocardial Imaging With Thallium-201 and Technetium-99m Pyrophosphate**

FRANS J. TH. WACKERS, K. I. LIE, ELLINOR BUSEMANN SOKOLE, JAN RES, JAN B. VAN DER SCHOOT and DIRK DURRER

Thallium-201 and technetium-99m pyrophosphate myocardial imaging studies in 78 consecutive patients with acute inferior wall infarction revealed right ventricular involvement but no signs of severe right ventricular failure. Some may have had subclinical right ventricular dysfunction. In patients with acute inferior wall infarction and signs of severe pump failure, dual imaging with these agents provides a simple noninvasive method of recognizing the subgroup of patients with hemodynamic deterioration due to major right ventricular involvement. Appreciation of the condition and subsequent appropriate treatment with volume loading may be life-saving in this group who classically show low cardiac output and elevated right ventricular pressures responding with an increase of cardiac output on volume loading.

Continued on page A13

*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy. Tablets of 25 mg.

For complete details, please see the full prescribing information.

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363 Metabolic Responses of the Heart in Acute Myocardial Infarction in Man

HILTRUD S. MUELLER, and STEPHEN M. AYRES

Acute myocardial infarction evokes a characteristic neurohumoral response in which catecholamine release is increased, plasma contents of free fatty acids and glucose are elevated and glucose tolerance is diminished. A total of 173 metabolic studies of the myocardium initiated during the first 12 hours of myocardial infarction were performed in 50 patients with acute transmural infarction. Forty-one percent showed a pattern of predominant myocardial free fatty acid uptake in the presence of elevated plasma free fatty acid and glucose contents; 21 percent revealed normal myocardial metabolism; 18 percent showed enhanced carbohydrate uptake; 20 percent showed high plasma substrate uptake suggesting metabolic breakdown. In this study patients with high plasma catecholamine and free fatty acid contents with increased myocardial free fatty acid uptake and lowered myocardial respiratory quotient had more complications than those with predominant carbohydrate or normal metabolic patterns. Because salvage of the endangered myocardium has a major priority, dampening of the sympathetic response with beta adrenergic blockade appears promising for most patients without evidence of significant ventricular failure.

372 Exercise Training and Plasma Catecholamines in Patients With Ischemic Heart Disease

JON D. COOKSEY, PATRICIA REILLY, SANDRA BROWN, HOWARD BOMZE and PHILIP E. CRYER

This study of a 3 month program of exercise training in 10 patients with ischemic heart disease supports the conclusion that regular exercise training reduces the myocardial oxygen cost of a given exercise load, as reflected by a decreased heart rate-systolic arterial pressure product at a given level of exercise. The maximal heart rate-systolic arterial pressure product attained with maximal treadmill exercise was increased in 6 of the 10 subjects. After exercise training patients showed a significant reduction in plasma norepinephrine during supine rest and a decrease in epinephrine and norepinephrine at a given level of treadmill exercise. These findings suggest that the adaptation of the cardiovascular system to exercise training is partially mediated by way of the sympathetic nervous system and is reflected by a reduced output of catecholamines at a given work level. Sympathetic activity is better tolerated in trained patients who can attain higher levels of maximal heart rate, blood pressure and plasma catecholamine concentration after regular exercise training.

377 Slow Filling Period/Rapid Filling Period Ratio in the Apexcardiogram: Relation to the Diagnosis of Coronary Artery Disease

AGENOR SILVESTRE, GURMIT SANDHU, KENNETH B. DESSER and ALBERTO BENCHIMOL

Analysis of apexcardiograms in 68 consecutive patients with normal findings of coronary artery disease on cardiac catheterization indicate that the slow/rapid filling period ratio is a useful noninvasive measurement for identifying subjects with ischemic heart disease. Increased values associated with obstructive coronary lesions may be caused by impairment of early left ventricular distensibility. This ratio should be determined in patients with other forms of heart disease to determine its specificity. These data suggest that the ratio of slow filling period to rapid filling period frequently (in 86 percent of the patients) exceeds 2.8 in patients with angiographically demonstrated occlusive coronary artery disease and identifies 94 percent of patients with a left ventricular end-diastolic pressure greater than 12 mm Hg. This externally derived measurement appears to be more sensitive than the a/H ratio for ascertaining the presence or absence of coronary atherosclerosis in patients with chest pain.

383 Mitral Valve Motion and Changes in Left Ventricular End-Diastolic Pressure: A Correlative Study of the PR-AC Interval

J. RANDOLPH LEWIS, JOHN O. PARKER and GARY W. BURGGRAF

Manipulating left ventricular end-diastolic pressure in 22 patients undergoing cardiac catheterization while recording the mitral valve echogram, these investigators found the PR-AC interval of limited value in predicting abnormal values or serial changes in left ventricular end-diastolic pressure. In the resting state a PR-AC interval greater than 0.06 second correctly predicted a left ventricular end-diastolic pressure of less than 20 mm Hg in 15 of 16 subjects. A short PR-AC interval (0.06 second or less) incorrectly predicted a left ventricular end-diastolic pressure greater than 20 mm Hg in four of six subjects. A poor correlation was found between the PR-AC interval and left ventricular end-diastolic pressure after maneuvers that increased or decreased left ventricular end-diastolic pressure.

Continued on page A17

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*All values given in this example are approximations based on standard physiologic data and solute-volume relationships.

†From a baseline of 80 mm. Hg diastolic.

BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema.

Contraindications: Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.

Warnings: Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.

Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

Adverse Reactions: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

Usual Dose: One tablet daily.

How Supplied: Tablets—100 mg. (white, scored) and 50 mg. (aqua) in bottles of 100 and 1000; PAKs of 28 tablets, boxes of 6; unit-dose blister packs, boxes of 100 (10 x 10 strips).

References:

1. Guyton, A.C.: Regulation of arterial pressure: II. The renal-body fluid system for long-term pressure control. Mechanisms of hypertension, in Textbook of Medical Physiology, Philadelphia, Saunders, 1976, p. 281. **2.** Kaplan, N.: Treating hypertension: The results are in, in Mandates Hypertension (Kaplan, N.M., ed.), New York, Medcom, 1976, p. 6. **3.** Finnerty, F.A., Jr.: Hypertension: The Continuing Challenge, Scientific Exhibit, Meeting of AAFP, Boston, Mass., Sept. 20-23, 1976. **4.** Fries, E.D.: The treatment of hypertension: Why, when and how, in Hypertension Manual (Laragh, J.H., ed.), New York, Dun-Donnelley, 1974, p. 751. **5.** Tarazi, R.C.: Modern concepts in diuretic therapy, Postgrad. Med. 56:37, 1974

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SUMMARY OF PRESCRIBING INFORMATION

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

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Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.

Precautions: Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe response can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: *Individual Dose:* To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg.

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CONTENTS

388 Echocardiography: Pericardial Thickening and Constrictive Pericarditis

INGELA SCHNITTGER, ROBERT E. BOWDEN, JACK ABRAMS and RICHARD L. POPP

Although present criteria for pericardial thickening on M mode echocardiography include several patterns consistent with pericardial thickening, these are not specifically pathognomonic of constrictive pericardial disease. In this study seven echocardiographic patterns consistent with pericardial adhesions or pericardial thickening were found in 167 patients. The hemodynamic diagnosis of constrictive pericardial disease in these patients was associated with the echocardiographic finding of pericardial thickening, but there were no consistent echocardiographic patterns of pericardial thickening diagnostic of constriction. Certain other echocardiographic abnormalities of left ventricular posterior wall motion and interventricular septal motion and a high E-F_o slope were found suggestive of constriction. This appearance, together with pericardial thickening, especially in a patient without known cause of pericardial thickening, strongly suggests constrictive pericarditis.

396 Carotid Sinus Hypersensitivity and Syncope

PAUL F. WALTER, I. SYLVIA CRAWLEY and EDWARD R. DORNEY

Although the hyperactive carotid sinus reflex is estimated to be found in approximately one third of older men with coronary atherosclerotic and hypertensive heart disease, most such patients are asymptomatic. This study of 21 men with episodes of lightheadedness or syncope, or both, associated with a hypersensitive carotid sinus reflex revealed the cardioinhibitory type in 17, the vasodepressor type in 2 and a combination of both types in 2. The insertion of a permanent pacemaker benefited the patients with the cardioinhibitory type with multiple episodes of syncope. Electrophysiologic studies in 17 patients with the cardioinhibitory type suggest that intrinsic sinus nodal dysfunction is not the major cause for asystole after carotid sinus stimulation. The results of sinus nodal recovery time in these patients were of little value in selecting patients for pacemaker therapy.

404 Initiation of Two Distinct Forms of Atrioventricular Nodal Reentrant Tachycardia During Programmed Ventricular Stimulation in Man

RUEY J. SUNG, JANUARIUSZ L. STYPEREK, ROBERT J. MYERBURG and AGUSTIN CASTELLANOS

During the study of eight patients with supraventricular tachycardia two distinct forms of A-V nodal reentrant tachycardia were elicited during programmed ventricular stimulation: (1) a slow-fast form using a slow A-V nodal pathway for anterograde conduction and a fast A-V nodal pathway for retrograde conduction, and (2) a fast-slow form with a tachycardia circuit in a reversed direction. Their initiation depended on differences in the electrophysiologic properties of fast and slow A-V nodal pathways during retrograde conduction. This phenomenon occurred in 8 of 42 patients with paroxysmal supraventricular tachycardia associated with dual A-V nodal pathway conduction. This study also demonstrated that both forms of A-V nodal reentrant tachycardia can be elicited from the atria as well as from the ventricles.

416 Sustained Ventricular Tachycardia: Evidence for Protected Localized Reentry

MARK E. JOSEPHSON, LEONARD N. HOROWITZ, ARDESHIR FARSHIDI, SCOTT R. SPIELMAN, ERIC L. MICHELSON and ALLAN M. GREENSPAN

Evaluation of 26 patients in whom sustained ventricular tachycardia could be reproducibly initiated or terminated, or both, suggests that the reentrant circuit must be small, electrocardiographically silent and relatively protected. The His bundle, proximal His-Purkinje system and the major portions of the ventricles appear not to be incorporated in the reentrant pathway. The bulk of evidence still suggests that sustained ventricular tachycardia that can be reproducibly initiated or terminated, or both, with programmed stimulation is due to reentry, although triggered automaticity as a mechanism of ventricular tachycardia cannot be totally excluded in all patients.

EXPERIMENTAL STUDIES

425 Precordial Mechanical Stimulation for Exposing Electrical Instability in the Ischemic Heart

BERNARD LOWN, RICHARD L. VERRIER and CHARLES M. BLATT

After experimentally produced coronary arterial occlusion in dogs, sequential mechanical pulsing of the chest wall with three stimuli evoked in 11 of 12 animals repetitive ventricular responses, including ventricular fibrillation in 7 and ventricular tachycardia in 2. Precordial pulsing induced repetitive ventricular arrhythmias in four

Continued on page A19

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conscious animals after their recovery from myocardial infarction. The basis for the effectiveness of the mechanical stimulus is that it depolarizes myocardial fibers by transduction of the mechanical pulse into an electrical depolarization, the heart responding as a mechanoelectrical transducer. Adapting this technique of precordial mechanical stimulation to elicit a single repetitive ventricular response may be a method of detecting patients at high risk for sudden cardiac death from malignant ventricular arrhythmias.

429 **Progressive Transmural Electrographic, Myocardial Potassium Ion/Sodium Ion Ratio and Ultrastructural Changes As a Function of Time After Acute Coronary Occlusion**

VIDYA S. BANKA, MONTY M. BODENHEIMER, KODANGUDI B. RAMANATHAN, GEORGE A. HERMANN and RICHARD H. HELFANT

These data in eight dogs after experimentally produced acute coronary occlusion show the dynamic evolution of an acute myocardial infarction involves a sequential progression from endocardium to epicardium as a function of time, resulting in an epicardial "border zone" in the early stages after the infarction. The process of infarction within the central zone is nonhomogeneous. In the early stages the epicardial layer of the central zone exhibits characteristics of a true border zone, and viable and salvageable myocardium may exist in the central and surrounding border zones. The salvageability may depend on the time elapsed after the coronary occlusion, myocardial oxygen requirements and the availability of accessory blood supply.

METHODS

444 **Computer-Assisted Reporting System for the Follow-Up of Patients With Prosthetic Heart Valves**

DAVID C. MacGREGOR, H. DOMINIC COVVEY, GREGORY J. WILSON, LEONARD SCHWARTZ, HUGH E. SCULLY and E. DOUGLAS WIGLE

This comprehensive computer-assisted data collection, management and reporting system was developed and successfully used to provide adequate follow-up of more than 2,000 prosthetic valve operations. Such computer-assisted methodology permits direct access to relevant information and helps to create an environment in which essential research can be carried out in the face of demanding clinical practice.

453 **Transvascular Endomyocardial Biopsy in Infants and Small Children: Description of a New Technique**

PAUL R. LURIE, MASAHIRO FUJITA and HARRY B. NEUSTEIN

First developed in small dogs and then proved safe and effective in rabbits weighing 3 kg, this miniaturized technique for transcatheter endomyocardial biopsy detailed in this report was safely performed in 10 children aged 4 1/2 months to 5 1/2 years. None had a biopsy-related complication except for an anemia in one patient. One or two premature ventricular contractions occurred in each patient at the moment the specimens were taken. The additional time to take six specimens averaged about 1 hour.

PEDIATRIC CARDIOLOGY

458 **Life Expectancy Without Surgery in Tetralogy of Fallot**

ENRIQUE G. BERTRANOU, EUGENE H. BLACKSTONE, JANE B. HAZELRIG , MALCOLM E. TURNER, Jr. and JOHN W. KIRKLIN

Survival data obtained from all published autopsy cases of patients with tetralogy of Fallot who died without surgical treatment and Danish data on living persons with tetralogy of Fallot in 1949 indicate that 66 percent of such patients live to age 1 year, 49 percent to age 3 years and 24 percent to age 10 years. Thereafter, the hazard function remains constant. The data support the generally accepted concept that the natural history of persons born with tetralogy of Fallot is determined primarily by the severity of the pulmonary stenosis, as demonstrated by the tendency of persons with pulmonary atresia to die at a younger age than those without pulmonary atresia or the group as a whole. Because about one half of surgically untreated patients with tetralogy of Fallot die in the first 2 years of life, surgical programs for persons with this malformation should include techniques for surgical intervention in the early months and years of life.

Continued on page A21

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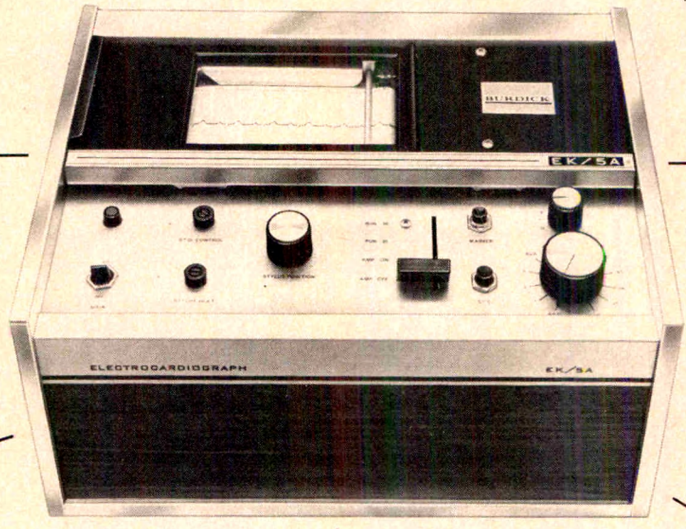

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467 Association of Interrupted Aortic Arch With Malformations Producing Reduced Blood Flow to the Fourth Aortic Arches

G. WILLIAM MOORE and GROVER M. HUTCHINS

This postmortem examination of the hearts of 12 patients with interrupted aortic arch, a rare congenital malformation of the great arteries with loss of continuity between the proximal portion of the aortic arch and the descending aorta, suggests that this condition is associated with malformations of the heart and great arteries that produce a reduced blood flow to the embryonic fourth aortic arches. Typically there is an interventricular communication and pathway of the ductus arteriosus through which flow passes into the descending aorta. The 12 hearts could be classified into four categories: 7 with normally formed A-V valves and a significant pulmonary arterial override over the ventricular septal defect; 2 with significant mitral valve obstruction but normally formed outflow tracts; 2 with double inlet left ventricle and transposition of the great arteries; and 1 with truncus arteriosus malformation. Interrupted aortic arch may be due to the disappearance of the normally persisting connection between the fourth and sixth arches as a result of flow imbalance in early cardiogenesis.

REPORTS ON THERAPY

473 Antiarrhythmic Drug Effect Assessed From Ventricular Arrhythmia Reduction in the Ambulatory Electrocardiogram and Treadmill Test: Comparison of Propranolol, Procainamide and Quinidine

ROGER A. WINKLE, ALAN H. GRADMAN and JOHN W. FITZGERALD. *With the technical assistance of* PATRICIA A. BELL

A 5 week study in 17 patients with frequent ventricular ectopic complexes showed that the ambulatory 24 hour electrocardiogram detected more qualitative types of ventricular arrhythmias than the exercise treadmill test. Of the three antiarrhythmic drugs tested, propranolol was associated with fewest side effects and procainamide with the most during short-term administration. Both quinidine and procainamide were more likely than propranolol to produce nearly complete suppression of arrhythmias. These data suggest that quinidine may be the most useful of the three drugs for suppressing asymptomatic ventricular ectopy in individual patients. Only 44 percent of 16 patients using this drug could have had 90 percent suppression of ventricular ectopic complexes without side effects. Additional studies appear indicated to demonstrate what level and what type of arrhythmia suppression, if any, correlate with a reduction in sudden death.

481 Reduced Quinidine Clearance in Elderly Persons

HERMANN R. OCHS, DAVID J. GREENBLATT, ELAINE WOO and THOMAS W. SMITH

This study demonstrates a significant prolongation of the elimination half-life (7.3 hours) of quinidine and a reduction in the rate of its total clearance in healthy volunteers aged 60 years or older compared with values in subjects aged 34 years or less. The rates of renal clearance of creatinine and quinidine were lower in the elderly and highly correlated. The results suggest that hepatic biotransformation and renal excretion of quinidine decrease with age. The choice of quinidine dose schedules in clinical practice should take into account the age of the patient. A decreased rate of quinidine clearance in the elderly could predispose to excessive drug accumulation and possibly toxicity unless doses are appropriately adjusted.

486 Efficacy of Lidocaine in Preventing Primary Ventricular Fibrillation Within 1 Hour After a 300 mg Intramuscular Injection. A Double-Blind, Randomized Study of 300 Hospitalized Patients With Acute Myocardial Infarction

K. I. LIE, KOEN L. LIEM, WILLEM J. LOURIDTZ, MICHIEL J. JANSE, ALBERTUS F. WILLEBRANDS and DIRK DURRER

The incidence of major ventricular arrhythmias in the first 60 minutes after the injection of lidocaine or sodium chloride placebo and the mortality rate were equal in both the treated and control groups of 300 patients admitted to the hospital within 6 hours of myocardial infarction. The ineffectiveness of the intramuscular injection of 300 mg of lidocaine is attributed to the inadequate blood levels attained by this dose. Lidocaine caused no major side effects such as respiratory arrest or epileptic seizures, but nine patients showed drowsiness, numbness of tongue and lips or speech disturbances. All deaths occurred after termination of the trial. These data suggest that a larger lidocaine dose seems to be required to prevent primary ventricular fibrillation than to suppress ventricular ectopic complexes.

Continued on page A23

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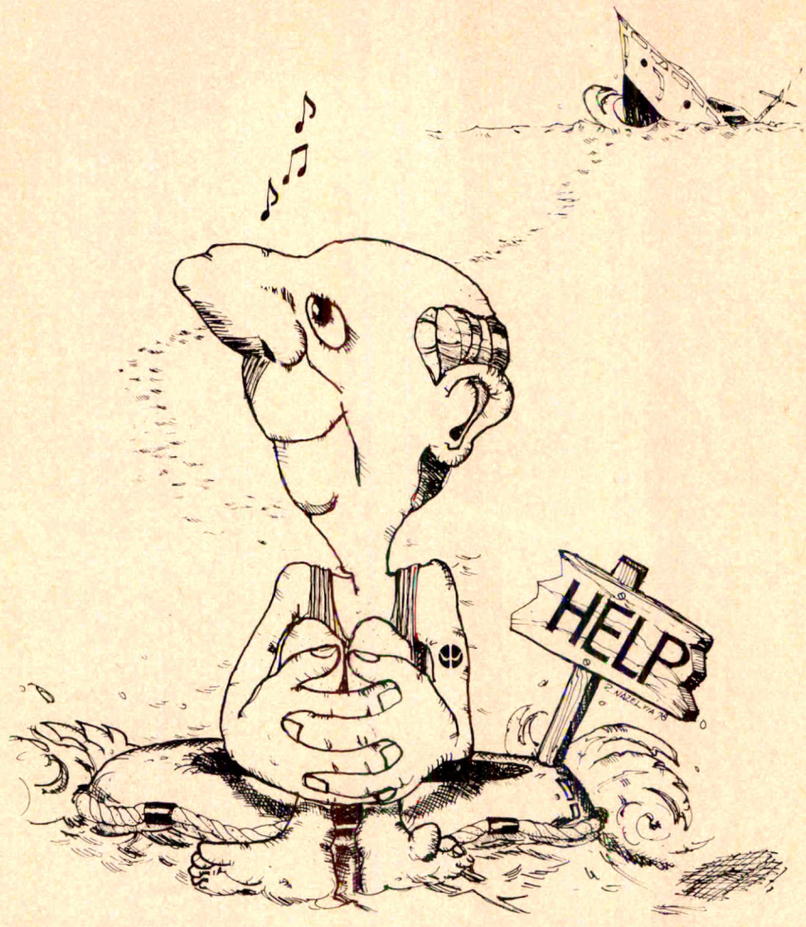

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EPIDEMIOLOGY

489 Natural History of Myocardial Infarction in the Coronary Drug Project: Long-Term Prognostic Importance of Serum Lipid Levels

CORONARY DRUG PROJECT RESEARCH GROUP

Data in 2,789 men in the Coronary Drug Project placebo group show a clear-cut significant relation between baseline serum cholesterol level and long-term prognosis for men recovered from myocardial infarction, but no such relation for serum triglycerides. Findings indicative of cardiovascular status at baseline evaluation, particularly the state of the myocardium, were even more powerful prognosticators than the level of serum cholesterol in these postmyocardial infarction patients. Safe nutritional means of reducing serum cholesterol may be useful after myocardial infarction as part of the total therapeutic regimen to improve long-term prognosis.

DIAGNOSTIC SHELF

499 Retrograde Block During Dual Pathway Atrioventricular Nodal Reentrant Paroxysmal Tachycardia

ROBERT A. BAUERNFEIND, DELON WU, PABLO DENES and KENNETH M. ROSEN

Electrophysiologic studies in two patients with second degree retrograde block during dual pathway A-V nodal reentrant paroxysmal tachycardia showed that the site of block was intraatrial in one and probably A-V nodal in the other. It is likely that the administration of procainamide played a role in the development of the intraatrial block. These studies also suggest that the atria are not a necessary part of the reentrant pathway and that A-V nodal reentry can occur only in patients with intact retrograde conduction. Although paroxysmal wide QRS tachycardia with retrograde block suggests ventricular tachycardia, these two patients demonstrate that a tachycardia of this type could be A-V nodal reentrant paroxysmal tachycardia.

506 Electrophysiologic Observations in a Patient With Bradycardia-Dependent Atrioventricular Block

DELON WU, PRAKASH DEEDWANIA, RAMESH C. DHINGRA, RICHARD M. ENGLEMAN and KENNETH M. ROSEN

This study demonstrates that bradycardia-dependent block can present with both sustained and paroxysmal atrioventricular (A-V) block. With bradycardia-dependent block the nonconducted impulses penetrate to the site of block and reset the state of membrane responsiveness. It also shows that second degree tachycardia-dependent block occurring at a proximal site (A-V node) associated with bradycardia-dependent block at a distal site can produce advanced second degree A-V block, as in this 62 year old patient with apparent tachycardia-dependent A-V block.

CASE REPORTS

513 Electrophysiologic Effects of Acute Myocardial Infarction in Man

ISAAC WIENER, BRUCE MINDICH and JOEL KUPERSMITH

A surface electrocardiogram and a bipolar electrogram from the left ventricle of a conscious patient recorded before and after development of a myocardial infarction showed areas of delayed epicardial action and diminution of local voltage. This serendipitous observation suggests that the electrophysiologic mechanisms of infarction in man are similar to those of infarction in the dog. This delay in epicardial activation may be important in the pathogenesis of reentrant ventricular arrhythmias.

517 Unusual Vasomotor Coronary Arterial Responses After Nitroglycerin

ROBERT L. FELDMAN, CARL J. PEPINE and C. RICHARD CONTI

Angiographic evidence of right coronary arterial narrowing after the administration of sublingual nitroglycerin in two patients argues against routine use of this agent before coronary arteriography. These unexpected vasomotor responses were unaccompanied by clinical complaints or chest pain. No explanation is offered for this coronary vasomotor response to nitroglycerin.

Continued on page A25

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529 American College of Cardiology News

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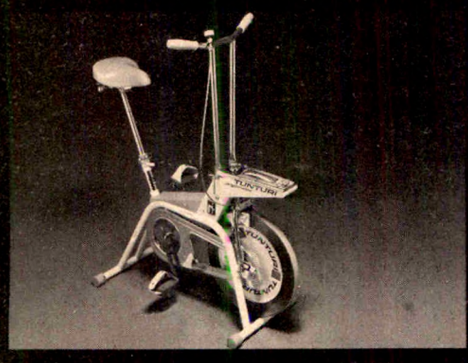
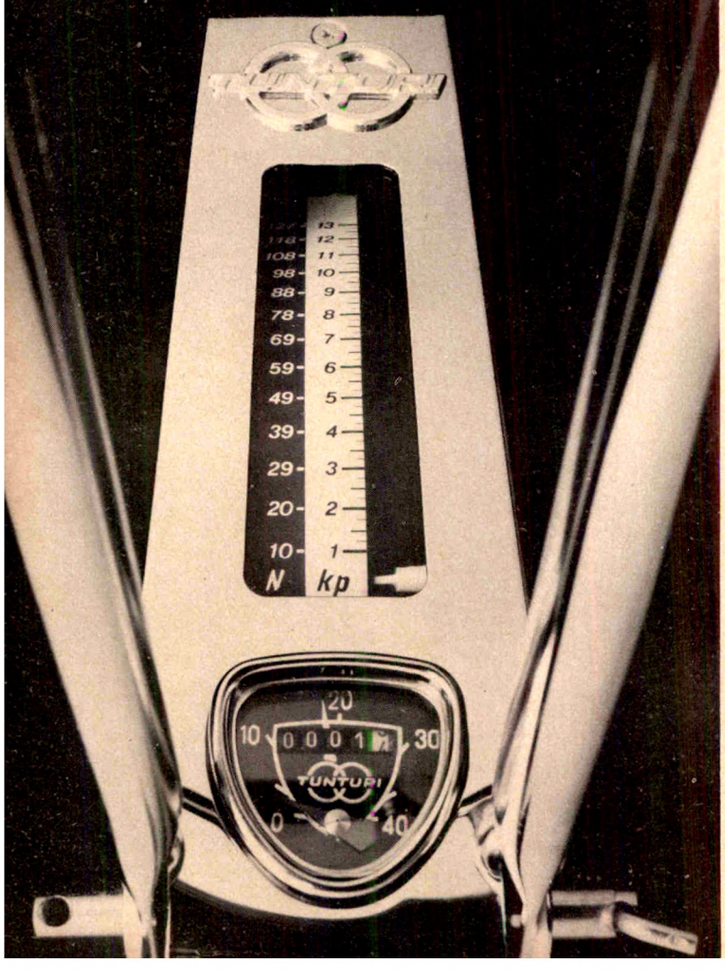


Controlled Exercise



PRONESTYL® TABLETS (Procainamide Hydrochloride Tablets)
PRONESTYL® CAPSULES (Procainamide Hydrochloride Capsules U.S.P.)

The prolonged administration of procainamide often leads to the development of a positive anti-nuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate considerations of alternative anti-arrhythmic therapy.

DESCRIPTION: Pronestyl (Procainamide Hydrochloride) is the amide analogue of procaine hydrochloride and is available for oral administration as capsules and veneer-coated tablets providing 250 mg., 375 mg., and 500 mg. procainamide hydrochloride.

CONTRAINDICATIONS: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; bear in mind cross sensitivity to procaine and related drugs. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of second degree and third degree A-V block unless an electrical pacemaker is operative.

ADMINISTRATION: Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

PRECAUTIONS: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous if myocardial damage exists.

The dislodgment of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in second degree and third degree A-V block, bundle branch block, or severe digitalis intoxication.

Bear in mind when treating ventricular arrhythmias in patients with severe organic heart disease and ventricular tachycardia that complete heart block, which may be difficult to diagnose, may be present. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; in event of rising titer (anti-nuclear antibody) or clinical symptoms of LE, assess the benefit/risk ratio related to continued procainamide therapy (see boxed Warning). Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

ADVERSE REACTIONS: Hypotension is rare with oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reported (see Precautions). Reactions consisting of fever and chills have been reported, including a case with nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy; and the patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever or any symptoms of upper respiratory tract infection. If any of these symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, and hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported.

The package insert should be read carefully to become familiar with the recommended dosage for the indicated conditions and for full prescribing information.

HOW SUPPLIED: Pronestyl Tablets (Procainamide Hydrochloride Tablets) and Pronestyl Capsules (Procainamide Hydrochloride Capsules U.S.P.) providing 250 mg., 375 mg., and 500 mg. are available in bottles of 100 and Unimatic® single-dose packaging in cartons of 100. The 250 mg. and 500 mg. tablets and capsules are also available in bottles of 1000.

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Documented effectiveness in ventricular arrhythmias; indicated for certain atrial arrhythmias as well.

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See preceding page for brief summary.

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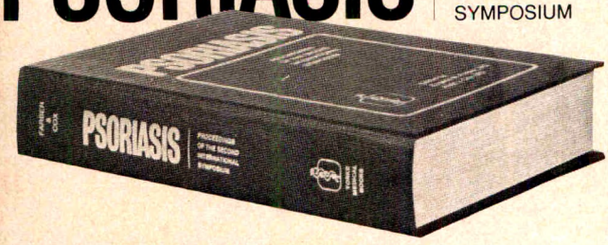

HELD IN JULY 1976 AT STANFORD UNIVERSITY ASSISTED BY THE NATIONAL INSTITUTE OF ARTHRITIS, METABOLISM, AND DIGESTIVE DISEASES

Edited by EUGENE M. FARBER, M.D.
Chairman, Department of Dermatology, Stanford University
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Professor of Pathology in Dermatology, Stanford University
in association with **Paul H. Jacobs,** M.D.,
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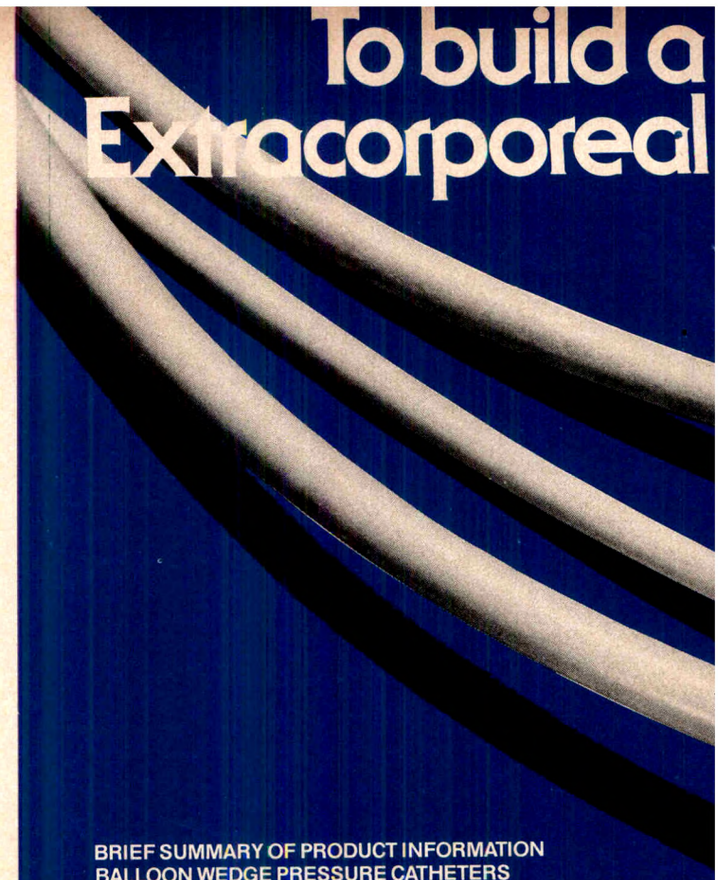
To build a Extracorporeal



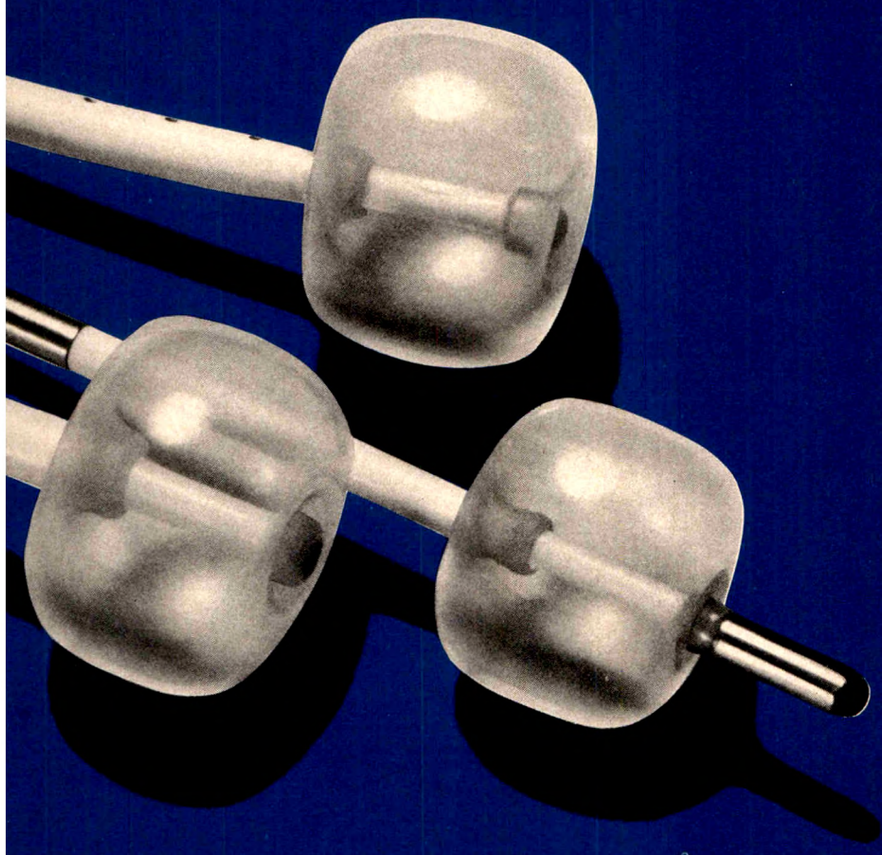
BRIEF SUMMARY OF PRODUCT INFORMATION
BALLOON WEDGE PRESSURE CATHETERS
Indications: For sampling blood for oxygen levels and measuring pressures in the right heart, including central venous, right ventricular, pulmonary artery, and pulmonary artery wedge pressure. Also indicated in anatomical cardiac defect cases to sample blood and measure pressures in any chambers that can be entered from the right heart. **Warning:** Pulmonary artery perforation, thrombosis, segmental pulmonary infarction, transient obstruction of the pulmonary outflow by the inflated balloon, balloon rupture without serious sequelae, premature ventricular contractions, and knotting of the catheter have been reported as complications of the use of balloon catheters. Balloon rupture with possible latex embolus is a potential complication in the use of balloon catheters. **Precaution:** In pressure monitoring at bedside when catheter has been introduced in an antecubital vein, patient's arm should be immobilized to reduce the possibility of catheter advancement due to arm motion.

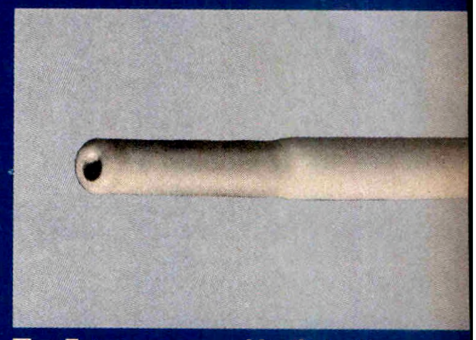
BERMAN ANGIOGRAPHIC CATHETER
Indications: For use in right-heart catheterization for cardiac angiography, pulmonary angiography, and measurement of right-heart and pulmonary artery pressures. It can be used to inject radiopaque media and measure pressures in any chambers and vessels that can be entered from the right heart. **Warnings:** Angiograms should be done with balloon inflated to minimize myocardial staining. When injecting radiopaque media, do not exceed stated maximum flow rate and pressure. Transient obstruction of the pulmonary outflow tract, balloon rupture without serious sequelae, premature ventricular contractions, and knotting of catheters are reported complication of the use of balloon catheters. Balloon rupture with possible latex embolus is a potential complication in the use of balloon catheters. **Precaution:** Manipulate catheter carefully and gently to avoid kinking or knotting.

BIPOLAR TEMPORARY PACING W/STYLET AND BALLOON TEMPORARY PACING CATHETERS
Indications: For temporary transvenous cardiac pacing when impulse formation or conduction is impaired. **Warnings:** Myocardial perforation, fibrillation and arrhythmia, pulmonary embolism, thrombus formation, and infection are general complications of transvenous pacing. Balloon rupture with possible latex embolus, vessel perforation, and intimal disruption are potential complications of use of balloon temporary pacing catheters. With the transbrachial approach, malpositioning and perforation occur more frequently due to arm movement. Pneumothorax, air embolism, and puncture of the subclavian artery have been reported with the subclavian approach. **Precautions:** Avoid kinking or bending catheter to prevent damage to internal wires or occlusion of inflation lumen (in balloon pacing catheter). Maintain insertion site with regular meticulous redressing performed with aseptic technique. Remove stylet from Bipolar Pacing Catheter after it is in position because leaving stylet *in situ* increases the potential for perforation..

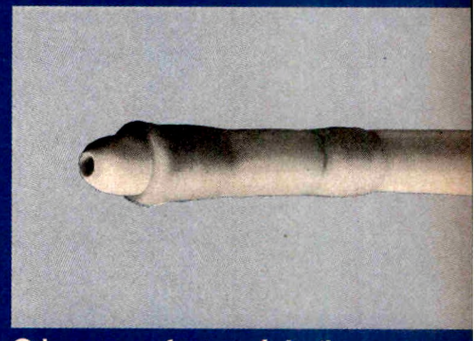
FOR BALLOON CATHETER USE, IN GENERAL
General Warnings: Carbon dioxide must be used to inflate balloon if there is a possibility that balloon rupture would result in air embolism in the left heart or systemic circulation. Do not inflate balloon beyond stated maximum inflation capacity. Exercise care when passing catheters in patients with left bundle-branch block because right bundle-branch block induced by traumatic catheter passage could result in complete heart block and asystole. **General Precautions:** Do not use liquids as balloon-inflation media. Pass catheter with continuous cardiographic monitoring and fluoroscopic guidance, and confirm final tip position by X-ray. Deflate balloon prior to withdrawing catheter to avoid possible valve damage. Use aseptic technique throughout procedure. All catheters are for single use only. Do not resterilize or reuse. Federal law (U.S.A.) restricts these devices to sale by or on the order of a physician. **Contraindication:** Not for use except as indicated.
For complete use information, see the package insert.

better cardiac catheter, starts with a built-in tip.





The Extracorporeal built-in tip, balloon deflated.



Other manufacturer's built-on tip, balloon deflated.

As you can see, the Extracorporeal tip is smooth, tapered, unruffled, suture free, no wider than the catheter itself. The benefits are built-in:

- **The introducer is the same size as the catheter.*** Not larger. This means a smaller insertion hole and less likelihood of trauma and intimal damage. And it simplifies introducer selection.
- **Less blood is lost.** Because the introducer is smaller and because the catheter fits it snugly the entire length of the catheter.
- **Our tapered tip has a larger lumen** which reduces the likelihood of clotting and makes it easier to introduce drugs and dyes.
- **A smaller diameter catheter may be used,** because a larger lumen also produces pressure measurements of a fidelity that can usually be matched only by a larger-diameter competitive catheter.
- **The tip is suture-free,** eliminating clotting caused by the sutures' irregular surface.

Beyond the tip, a host of other benefits.

- **Inflation is more convenient** because every Extracorporeal balloon catheter is packaged with an appropriately sized syringe.
- **Pure platinum electrodes for better electrical characteristics.** Blood may alter the conductivity properties of stainless steel and cause inferior readings. That's why our balloon pacing catheters employ only inert platinum for electrodes.
- **High pressure tubing** used in our Berman angiographic catheters permits higher pressures to be used to achieve better flow rates when drugs or dye must be injected.
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*With one small exception—the Extracorporeal 4F size uses a 4-1/2 size introducer.

extracorporeal

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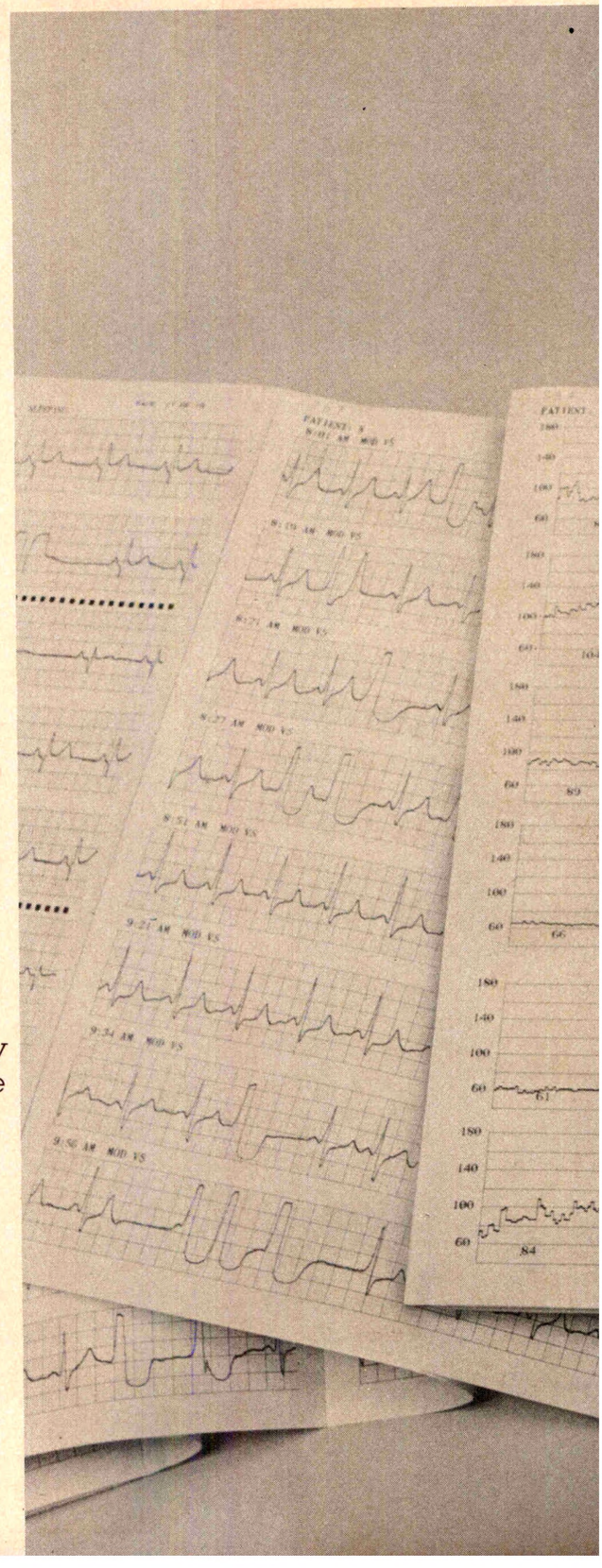

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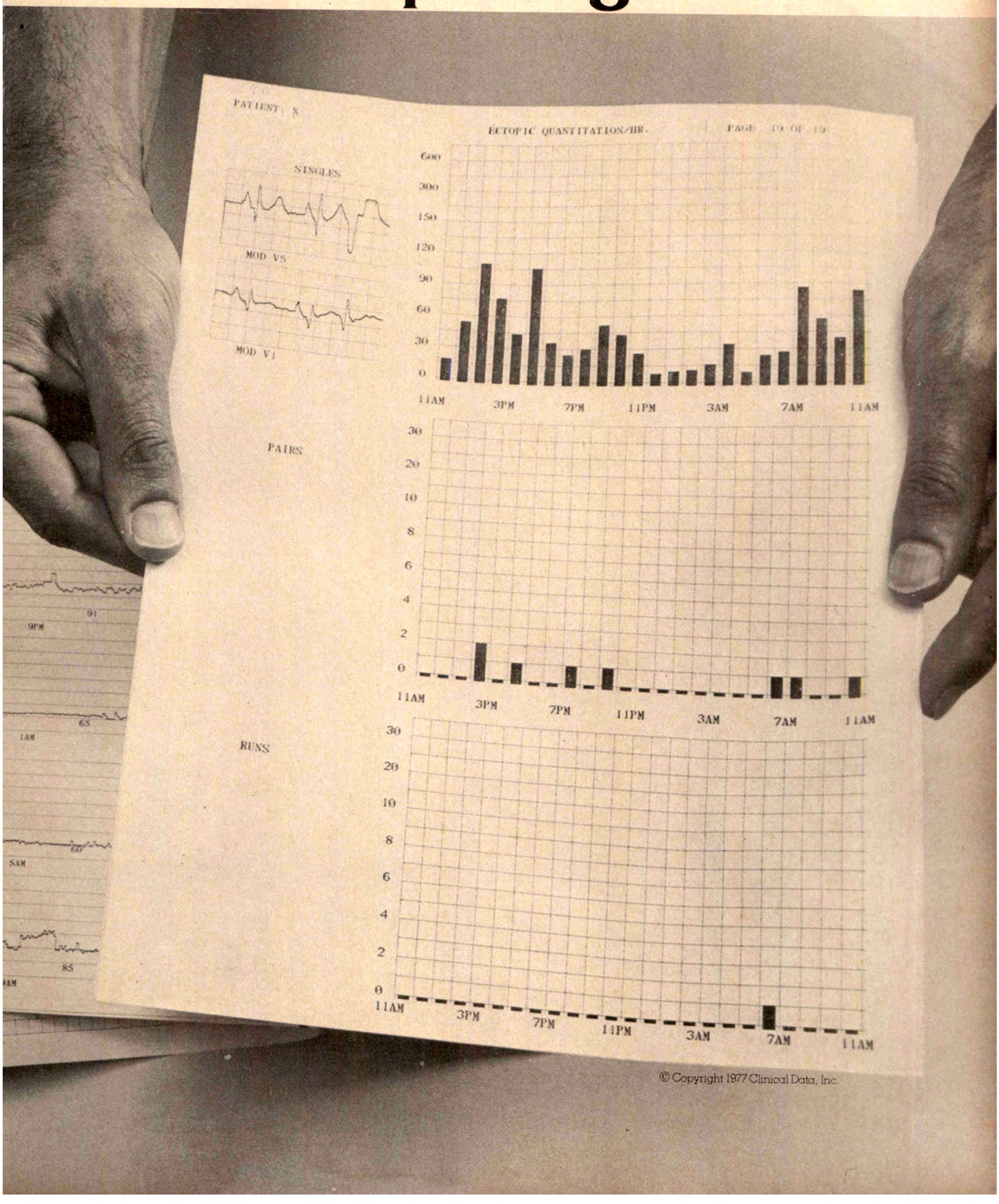

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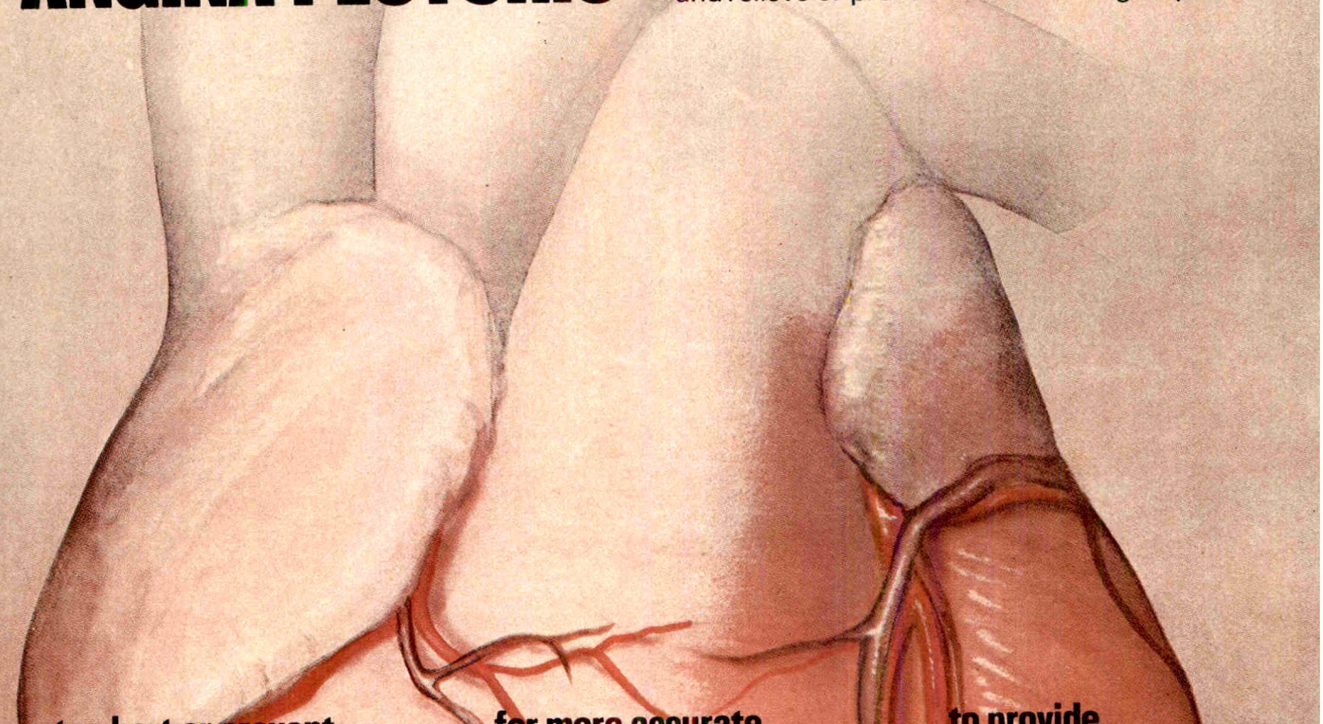
ISORDIL®
(isosorbide dinitrate)
HELPS THE HEART IN THE CONTROL OF ANGINA PECTORIS*

The established use of Isordil in the management of angina pectoris for more than two decades has often been ascribed only to the vasodilatation it produces in the coronary arteries. Recent investigations, however, suggest that an even more important effect of this agent is to dilate peripheral arteries and veins. Arterial dilatation lowers impedance to left ventricular ejection, reducing afterload. Venous dilatation leads to venous pooling and a fall in right and left ventricular filling pressure, thus reducing preload.

With afterload and preload reduced, the amount of energy expended and oxygen consumed by the heart should be decreased. Isordil can thus reduce myocardial oxygen requirements and relieve or prevent attacks of angina pectoris.



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to provide sustained prophylaxis against angina

ISORDIL® TEMBIDS® Capsules
Sustained-Action Capsules, 40 mg

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Probably" effective: When taken by the sublingual or chewable route, Isordil Sublingual and Chewable Tablets are indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.
"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Consult direction circular before prescribing.

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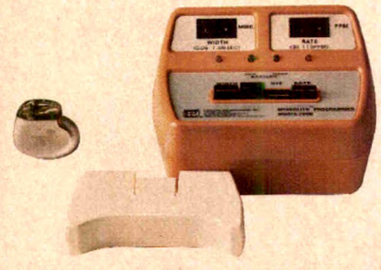
**Warranty statement available upon request*



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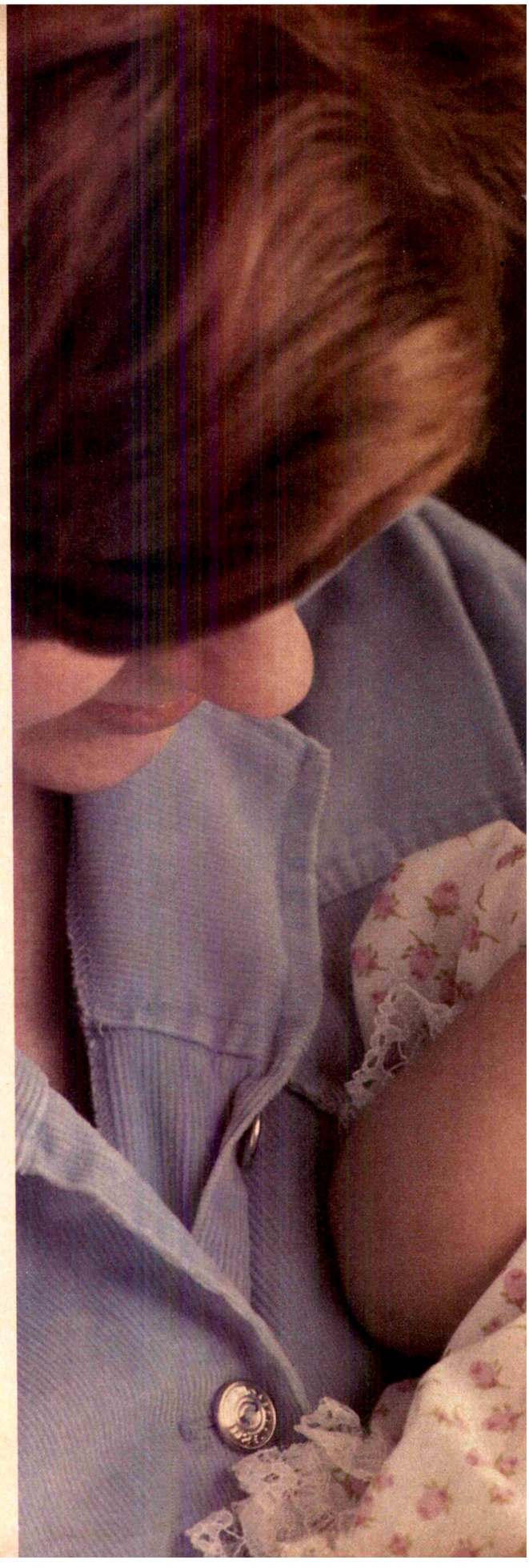
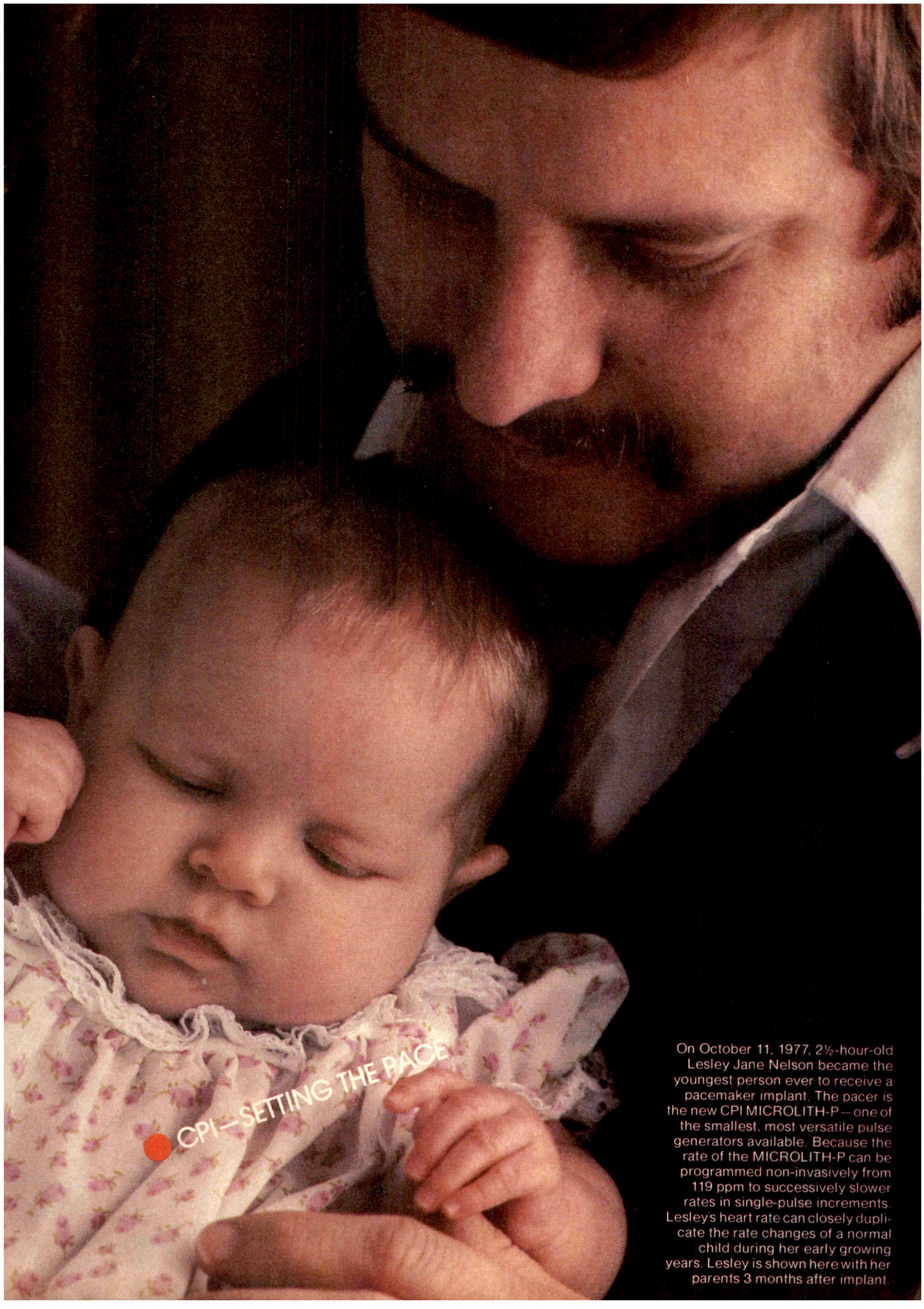
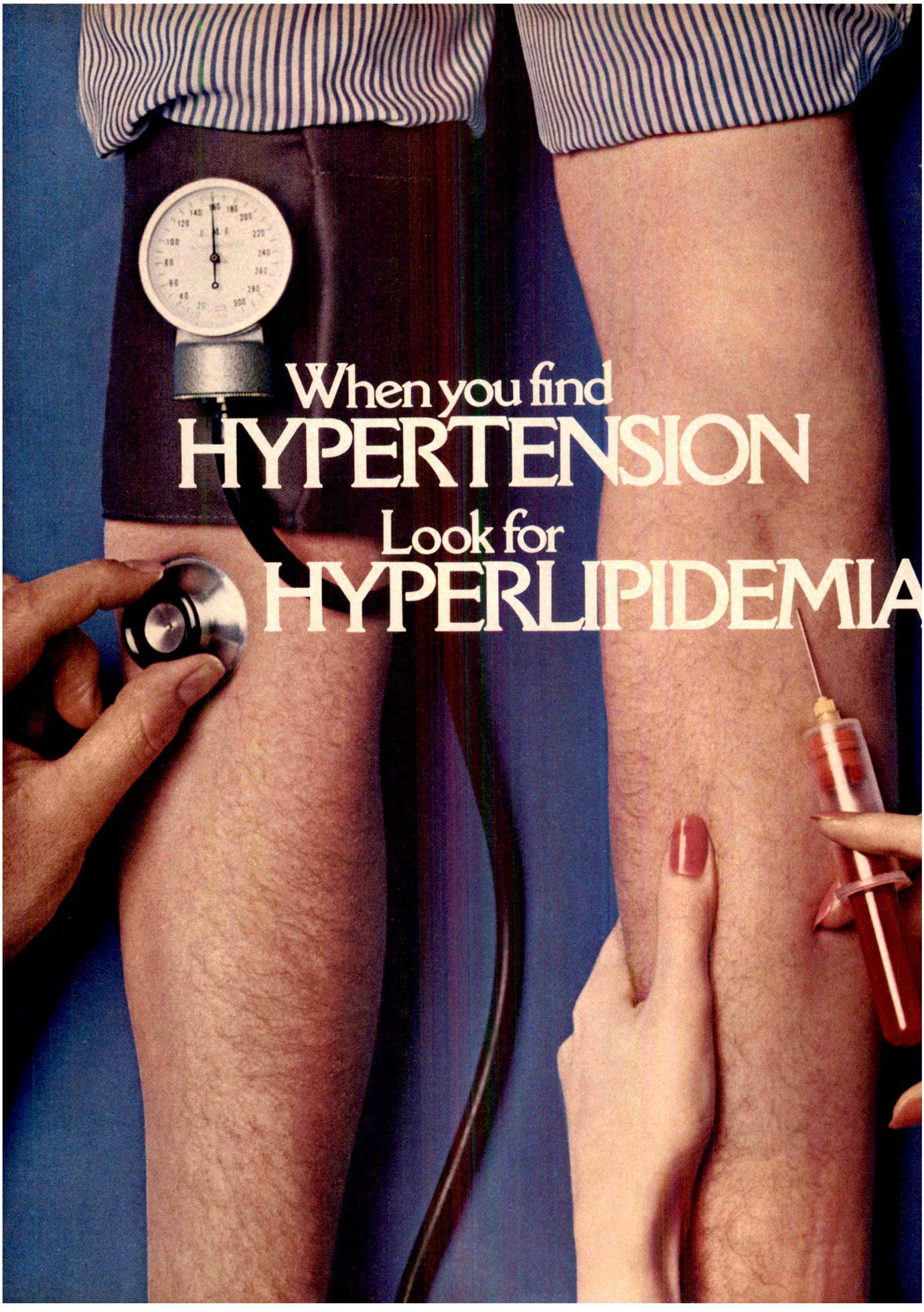




On October 11, 1977, 2½-hour-old Lesley Jane Nelson became the youngest person ever to receive a pacemaker implant. The pacer is the new CPI MICROLITH-P—one of the smallest, most versatile pulse generators available. Because the rate of the MICROLITH-P can be programmed non-invasively from 119 ppm to successively slower rates in single-pulse increments. Lesley's heart rate can closely duplicate the rate changes of a normal child during her early growing years. Lesley is shown here with her parents 3 months after implant.


When you find
HYPERTENSION
Look for
HYPERLIPIDEMIA

Two out of every five hypertensives found to be hyperlipidemic in recent study[1]

Lipid abnormalities are often part of a broader clinical picture. For example, a recent study[1] reports an association between hypertension and hypertriglyceridemia—the most common form of hyperlipidemia. (See table below.)

Type of Hyperlipidemia*	Incidence of Hyperlipidemia	
	Hypertensives (89 subjects)	Normotensives (89 subjects)
Type IIA	9% (8)	7% (6)
Type IIB	6% (5)	3% (3)
Type IV	26% (23)	11% (10)
Total	**41% (36)**	**21% (19)**

*Hyperlipidemia was diagnosed when cholesterol levels exceeded 282 mg% and /or triglycerides were over 177 mg%—cutoff points higher than the usual upper limits of normal.
Adapted from Thomas, G. W., *et al.*[1]

The essential measurements—cholesterol *and* triglycerides

Today, lipid determinations are recommended as part of every general medical examination.

Because elevated lipids may coexist with high blood pressure, it is especially important to screen hypertensive patients for hyperlipidemia. Testing for both cholesterol *and* triglycerides is considered essential,[2-5] since it increases the chances of detection from 6 out of 10 to 9.5 out of 10.[6]

AN IMPORTANT NOTE: It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

When diet alone is not enough

Atromid-S®

(clofibrate) Capsules 500 mg

significantly lowers serum levels of cholesterol and/or triglycerides

Proved effective in study after study

In clinical studies involving patients with drug-responsive hyperlipoproteinemia, diet plus ATROMID-S (clofibrate) lowered serum cholesterol levels from 22% to as much as 52% and reduced triglyceride values over a range of 19% to 80%.[7-12]

Patient acceptance is generally good

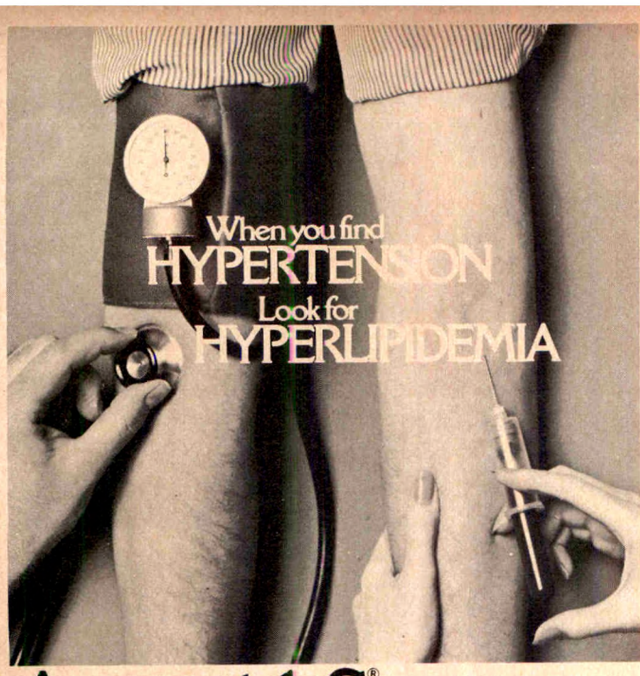
In more than a decade of use, clofibrate has been generally well tolerated. Major adverse effects are primarily gastrointestinal, with nausea being predominant. Other G.I. reactions include loose stools, flatulence, abdominal distress, and, infrequently, gallstones. Less common reactions include muscle cramping, myalgia, and alopecia. Please see "Important Note" at left and Warning on concomitant anticoagulant usage in prescribing information on following page.

The most widely prescribed antilipemic agent

Atromid-S® Ayerst

(clofibrate)

See next page of this advertisement for prescribing information.



Atromid-S® (clofibrate)

2 capsules b.i.d.

BRIEF SUMMARY

(For full prescribing information, see package circular.)

ATROMID-S® Brand of clofibrate

Antilipidemic agent for reduction of elevated serum lipids

INDICATIONS: ATROMID-S is indicated as adjunctive therapy in patients who do not respond adequately to diet and other measures for the reduction of elevated serum cholesterol (especially the beta lipoprotein fraction) and/or triglycerides. Clofibrate appears to have a greater depressant effect on the very low density lipoproteins (S_f 20-400) rich in triglycerides than the low density lipoproteins (S_f 0-20) rich in cholesterol.

ATROMID-S is also indicated for treatment of patients with xanthoma tuberosum associated with hyperlipidemia. The skin lesions frequently regress with clofibrate.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CONTRAINDICATIONS: Clofibrate is contraindicated in pregnant women. While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than that found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

It is contraindicated in lactating women since it is not known if clofibrate is secreted in the milk.

It is contraindicated in patients with clinically significant hepatic or renal dysfunction.

It is contraindicated in patients with primary biliary cirrhosis since it may raise the already elevated cholesterol in these cases.

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Strict birth control procedures must be exercised by women of childbearing potential. In patients who plan to become pregnant, clofibrate should be withdrawn several months before conception. Because of the possibility of pregnancy occurring despite birth control precautions in patients taking clofibrate, the possible benefits of the drug to the patient must be weighed against possible hazards to the fetus.

Administration of clofibrate to mice and rats in long-term studies at eight times the human dose resulted in a higher incidence of liver tumors than in controls. Lower doses were not studied. Although the relevance of this finding to humans is not known at this time, it cannot be dismissed especially since this drug is intended for long-term administration. ATROMID-S should be used only in patients with hyperlipidemia who do not respond adequately to dietary intervention.

PRECAUTIONS: Before instituting therapy with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.

Because of the long-term administration of a drug of this nature, adequate baseline studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be obtained during the first few months of ATROMID-S administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, the drug should be employed for longer periods (even up to one year) provided that there is a reduction in the size and/or number of the xanthomata.

Subsequent serum lipid determinations should be done to detect a paradoxical rise in serum cholesterol or triglyceride levels. Clofibrate will not alter the seasonal variations of serum cholesterol peak elevations in midwinter and late summer and decreases in fall and spring. If the drug is discontinued, the patient should be placed on an appropriate hypolipidemic diet, and his serum lipids should be monitored until stabilized, as a rise in these values to or above the original baseline may occur.

During clofibrate therapy, frequent serum transaminase determinations and other liver function tests should be performed since the drug may produce abnormalities in these parameters. These effects are usually reversible when the drug is discontinued. Hepatic biopsies are usually within normal limits. If the hepatic function tests steadily rise or show excessive abnormalities, the drug should be withdrawn. Therefore use with caution in those patients with a past history of jaundice or hepatic disease.

Clofibrate may produce "flu like" symptoms (muscular aching, soreness, cramping). The physician should differentiate this from actual viral and/or bacterial disease.

Use with caution in patients with peptic ulcer since reactivation has been reported. Whether this is drug-related is unknown.

Complete blood counts should be done periodically since anemia, and more frequently, leukopenia have been reported in patients who have been taking clofibrate.

Various cardiac arrhythmias have been reported with the use of clofibrate.

Several investigators have observed in their studies that clofibrate may produce a decrease in cholesterol linoleate but an increase in palmitoleate and oleate, the latter being considered atherogenic in experimental animals. The significance of this finding is unknown at this time.

ADVERSE REACTIONS: Of the pertinent reactions, the most common is nausea. Less frequently encountered gastrointestinal reactions are vomiting, loose stools, dyspepsia, flatulence, and abdominal distress. Reactions reported less often than gastrointestinal ones are headache, dizziness, and fatigue; muscle cramping, aching, and weakness; skin rash, urticaria, and pruritus; dry brittle hair, and alopecia.

The following reported adverse reactions are listed alphabetically by systems:

Cardiovascular
- Increased or decreased angina
- Cardiac arrhythmias
- Both swelling and phlebitis at site of xanthomas

Dermatologic
- Skin rash
- Alopecia
- Allergic reaction including urticaria
- Dry skin and dry brittle hair
- Pruritus

Gastrointestinal
- Nausea
- Diarrhea
- Gastrointestinal upset (bloating, flatulence, abdominal distress)
- Hepatomegaly (not associated with hepatotoxicity)
- Gallstones
- Vomiting
- Stomatitis and gastritis

Genitourinary
- Impotence and decreased libido
- Findings consistent with renal dysfunction as evidenced by dysuria, hematuria, proteinuria, decreased urine output. One patient's renal biopsy suggested "allergic reaction."

Hematologic
- Leukopenia
- Potentiation of anticoagulant effect
- Anemia
- Eosinophilia

Musculoskeletal
- Myalgia (muscle cramping, aching, weakness)
- "Flu like" symptoms
- Arthralgia

Neurologic
- Fatigue, weakness, drowsiness
- Dizziness
- Headache

Miscellaneous
- Weight gain
- Polyphagia

Laboratory Findings
- Abnormal liver function tests as evidenced by increased transaminase (SGOT and SGPT), BSP retention, and increased thymol turbidity
- Proteinuria
- Increased creatine phosphokinase

Reported adverse reactions whose direct relationship with the drug has not been established: peptic ulcer, gastrointestinal hemorrhage, rheumatoid arthritis, tremors, increased perspiration, systemic lupus erythematosus, blurred vision, gynecomastia, thrombocytopenic purpura.

DOSAGE AND ADMINISTRATION: *Initial:* The recommended dosage for adults is 2 g daily, in divided doses. Some patients may respond to a lower dosage.

Maintenance: Same as for initial dosage.

Note: In children, insufficient studies have been done to show safety and efficacy.

DRUG INTERACTIONS: Caution should be exercised when anticoagulants are given in conjunction with ATROMID-S. The dosage of the anticoagulant should be reduced usually by one-half (depending on the individual case) to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has been stabilized.

MANAGEMENT OF OVERDOSAGE: While there has been no reported case of overdosage, should it occur, symptomatic supportive measures should be taken.

HOW SUPPLIED: ATROMID-S—No. 243—Each capsule contains 500 mg clofibrate, in bottles of 100.

References: 1. Thomas, G. W., *et al.*: Br. Med. J. *2*:805 (Sept. 24) 1977. **2.** Ahrens, E. H., Jr.: Ann. Intern. Med. *85*:87 (July) 1976. **3.** Council on Foods and Nutrition: J.A.M.A. *222*:1647 (Dec. 25) 1972. **4.** Scheig, R.: Conn. Med. *39*:71 (Feb.) 1975. **5.** Letters to the Editor: Current Prescribing (July) 1977, p. 15. **6.** Fredrickson, D. S., *et al.*, in Holmes, W. L., Carlson, L. A., and Paoletti, R. (eds.): Drugs Affecting Lipid Metabolism, vol. 4, New York, Plenum Press, 1969, p. 314. **7.** Brown, H. B., Lewis, L. A., and Page, I. H.: Clin. Pharmacol. Ther. *17*:171 (Feb.) 1975. **8.** Gelfand, M. L., and Garbor, M.: Exhibit, American College of Cardiology Meeting, New Orleans, La., Feb. 21-Mar. 1, 1970. **9.** Zelis, R., *et al.*: J. Clin. Invest. *49*:1007 (May) 1970. **10.** Levy, R. I., *et al.*: Ann. Intern. Med. *77*:267 (Aug.) 1972. **11.** Berkowitz, D.: J.A.M.A. *218*:1002 (Nov. 15) 1971. **12.** Lorenzo, E. M., *et al.*: Curr. Ther. Res. *22*:147 (July, Sect. 2) 1977.

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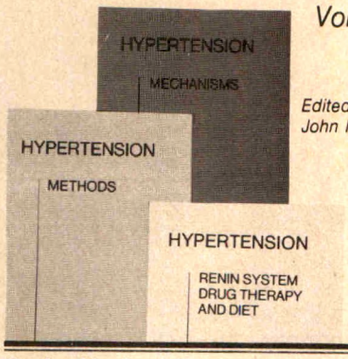

Edited by
John H. Laragh, MD

Master Professor of Medicine
Director of the Cardiovascular Center
The New York Hospital—Cornell Medical Center
and Founder of the Hypertension Center
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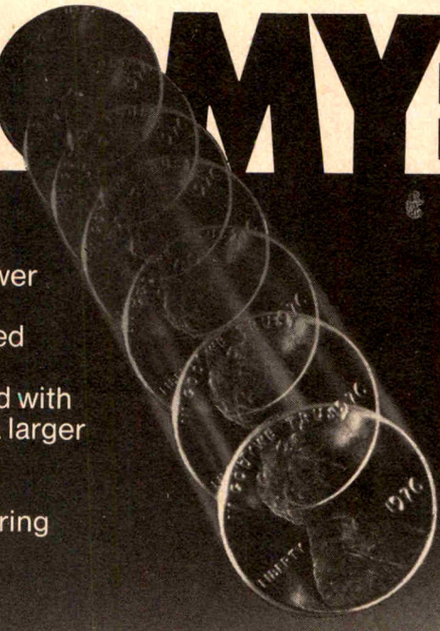

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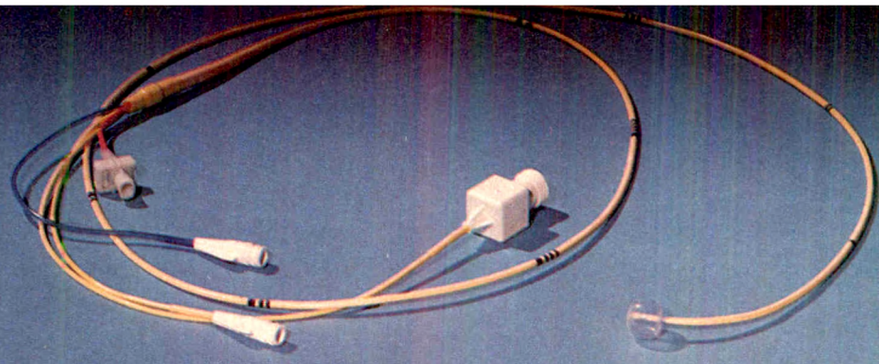

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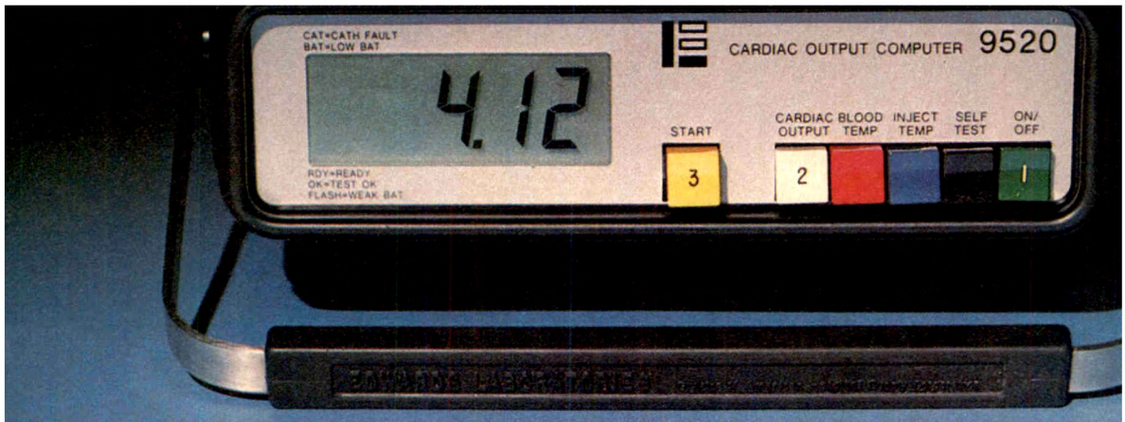

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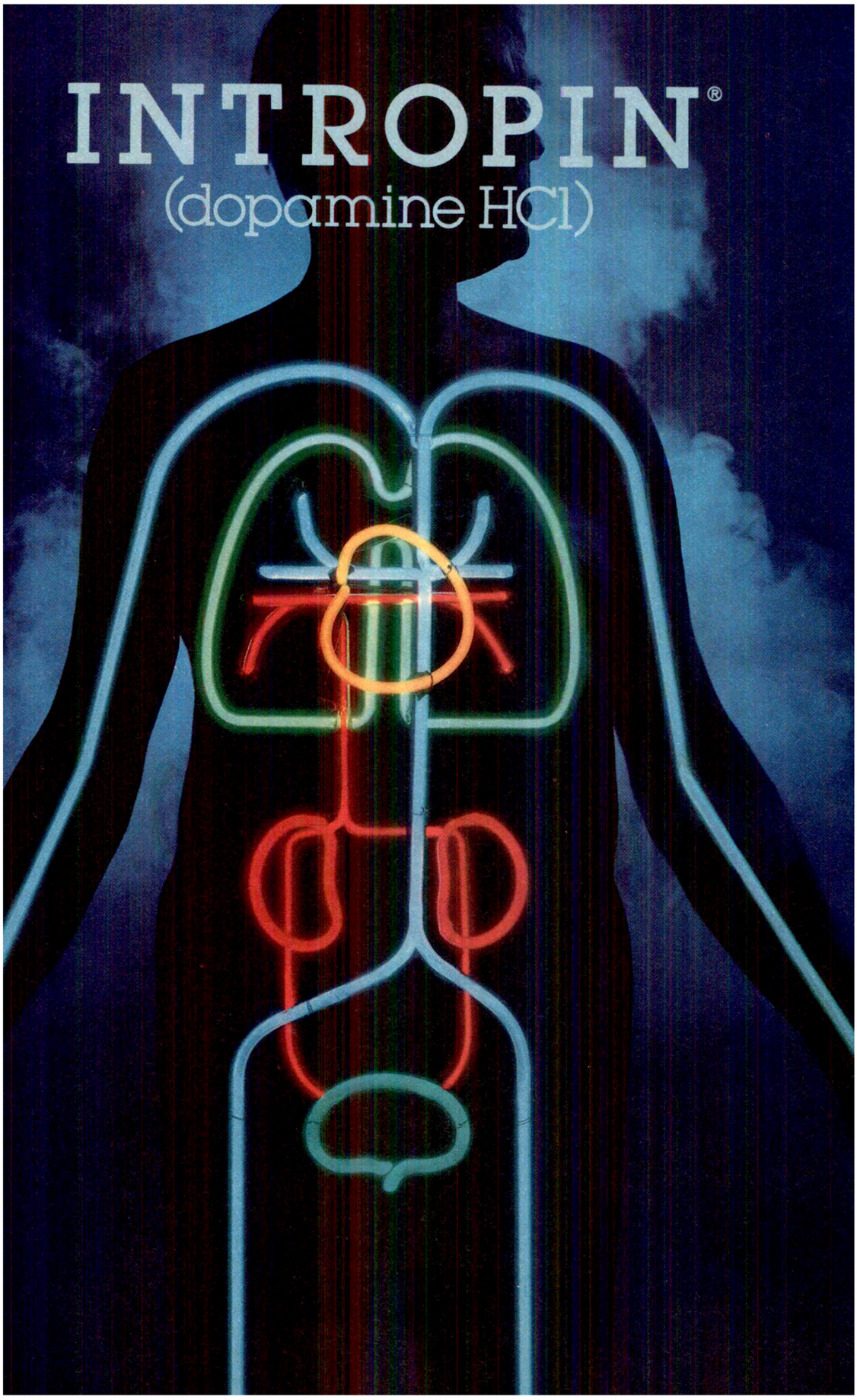
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In the shock syndrome:

Selectively redirects blood to vital organs

Increases vital organ perfusion

In the shock syndrome, perfusion pressure usually does not meet the metabolic needs of the vital organs. When volume replacement fails to reverse this process, additional therapy must be initiated to increase cardiac output and blood pressure and to increase blood flow to vital organs.

Intropin (dopamine HCl) is the only drug that both increases cardiac output and blood pressure while specifically redirecting the blood flow.

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The unique ability of Intropin to act on the "dopaminergic" receptors in the mesenteric and renal vasculature causes vasodilation in these beds and leads to increased renal blood flow, glomerular filtration rate and urine output. At low dose levels (less than 5 mcg/kg/min), when cardiac stimulation is not usually observed, these increases are independent of increased cardiac output.

In comparison, norepinephrine causes vasoconstriction in these beds, further compromising vital organ function.[1] Isoproterenol causes generalized systemic vasodilation (thereby requiring greater cardiac output to increase vital organ perfusion) and does not increase the renal fraction of the increased cardiac output.[2]

Increases cardiac output

At higher doses (above 5 mcg/kg/min), Intropin begins to increase myocardial contractility, stroke volume and cardiac output by direct positive inotropic effect while maintaining much of the unique dopaminergic effect. In certain patients such as refractory congestive failure patients, the increase in cardiac output may be seen at doses of less than 5 mcg/kg/min.

Norepinephrine, on the other hand, has a similar inotropic effect, but the expected increase in cardiac output is often diminished due to the increased systemic vascular resistance (afterload) resulting from norepinephrine's alpha adrenergic activity. Isoproterenol increases cardiac output in part through a chronotropic effect.[3] Its use results in a greater increase in myocardial oxygen consumption than does the inotropic effect of Intropin. It also results in a greater potential for arrhythmias.[3] The increased cardiac output obtained with isoproterenol is delivered to the total systemic vasculature due to general vasodilation while the selective vasodilation of Intropin directs more blood supply to the areas in need of vital perfusion.

Increases blood pressure

Intropin doses of over 20 mcg/kg/min will usually result in an alpha adrenergic (vasoconstriction) response in the peripheral vasculature. This usually raises the pressure and also redirects blood flow through the vasodilated vasculature of the renal and mesenteric beds. Thus, Intropin can increase blood pressure through an inotropic cardiac response or at doses above 20 mcg/kg/min through an additional peripheral vasculature response.

References:
1. Rosenblum, R., Am. Heart J., 87:527-530, 1974.
2. Goldberg, L.I., N.E.J. of Med., 291:707-710, 1974.
3. Harrison, D.C., Am. J. of Card., 35:656-659, 1975.

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INTROPIN® (dopamine HCl)

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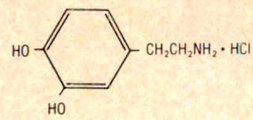


$C_8H_{11}NO_2 \cdot HCl$ Mol. Wt. 189.65

Dopamine hydrochloride is a white, odorless crystalline powder, freely soluble in water and soluble in alcohol. It is sensitive to light, alkalis, iron salts and oxidizing agents.

Each milliliter of sterile, pyrogen-free INTROPIN Injection contains 40 mg. of dopamine hydrochloride (equivalent to 32.96 mg. of dopamine base) in Water for Injection, USP, containing 1% sodium bisulfite as a preservative.

ACTIONS: INTROPIN exerts an inotropic effect on the myocardium resulting in an increased cardiac output. INTROPIN produces less increase in myocardial oxygen consumption than isoproterenol and its use is usually not associated with a tachyarrhythmia. Clinical studies indicate that INTROPIN usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure. Total peripheral resistance at low and intermediate therapeutic doses is usually unchanged. Blood flow to peripheral vascular beds may decrease while mesenteric flow increases. INTROPIN has also been reported to dilate the renal vasculature presumptively by activation of a "dopaminergic" receptor. This action is accompanied by increases in glomerular filtration rate, renal blood flow, and sodium excretion. An increase in urinary output produced by dopamine is usually not associated with a decrease in osmolality of the urine.

INDICATIONS: INTROPIN is indicated for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Where appropriate, restoration of blood volume with a suitable plasma expander or whole blood should be instituted or completed prior to administration of INTROPIN.

Patients most likely to respond adequately to INTROPIN are those in whom physiological parameters, such as urine flow, myocardial function, and blood pressure, have not undergone profound deterioration. Multiclinic trials indicate that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and INTROPIN, the better the prognosis.

Poor Perfusion of Vital Organs – Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. Nevertheless, the physician should also observe the patient for signs of reversal of confusion or comatose condition. Loss of pallor, increase in toe temperature, and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Clinical studies have shown that when INTROPIN is administered before urine flow has diminished to levels approximately 0.3 ml./minute, prognosis is more favorable. Nevertheless, in a number of oliguric or anuric patients, administration of INTROPIN has resulted in an increase in urine flow which in some cases reached normal levels. INTROPIN may also increase urine flow in patients whose output is within normal limits and thus may be of value in reducing the degree of pre-existing fluid accumulation. It should be noted that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Concurrent administration of INTROPIN and diuretic agents may produce an additive or potentiating effect.

Low Cardiac Output – Increased cardiac output is related to INTROPIN's direct inotropic effect on the myocardium. Increased cardiac output at low or moderate doses appears to be related to a favorable prognosis. Increase in cardiac output has been associated with either static or decreased systemic vascular resistance (SVR). Static or decreased SVR associated with low or moderate increments in cardiac output is believed to be a reflection of differential effects on specific vascular beds with increased resistance in peripheral beds (e.g. femoral) and concomitant decreases in mesenteric and renal vascular beds. Redistribution of blood flow parallels these changes so that an increase in cardiac output is accompanied by an increase in mesenteric and renal blood flow. In many instances the renal fraction of the total cardiac output has been found to increase. Increase in cardiac output produced by INTROPIN is not associated with substantial decreases in systemic vascular resistance as may occur with isoproterenol.

Hypotension – Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of INTROPIN, which have little effect on SVR. At high therapeutic doses, INTROPIN's alpha adrenergic activity becomes more prominent and thus may correct hypotension due to diminished SVR. As in the case of other circulatory decompensation states, prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, it is suggested that the physician administer INTROPIN as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

CONTRAINDICATIONS: INTROPIN should not be used in patients with pheochromocytoma.

WARNINGS: INTROPIN should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

Do **NOT** add INTROPIN to any alkaline diluent solution, since the drug is inactivated in alkaline solution.

Patients who have been treated with monamine oxidase (MAO) inhibitors prior to the administration of INTROPIN will require substantially reduced dosage. Dopamine is metabolized by MAO, and inhibition of this enzyme prolongs and potentiates the effect of INTROPIN. The starting dose in such patients should be reduced to at least one-tenth (1/10) of the usual dose.

Usage in Pregnancy – Animal studies have revealed no evidence of teratogenic effects from INTROPIN. In one study, administration of INTROPIN to pregnant rats resulted in a decreased survival rate of the newborn and a potential for cataract formation in the survivors. The drug may be used in pregnant women when, in the judgment of the physician, the expected benefits outweigh the potential risk to the fetus.

Usage in Children – The safety and efficacy of this drug in children has not been established. INTROPIN has been used in a limited number of pediatric patients, but such use has been inadequate to fully define proper dosage and limitations for use. Further studies are in progress.

PRECAUTIONS: Avoid Hypovolemia – Prior to treatment with INTROPIN, hypovolemia should be fully corrected, if possible, with either whole blood or plasma as indicated.

Decreased Pulse Pressure – If a disproportionate rise in the diastolic pressure (i.e. a marked decrease in the pulse pressure) is observed in patients receiving INTROPIN, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

Extravasation – INTROPIN should be infused into a large vein whenever possible to prevent the possibility of extravasation into tissue adjacent to the infusion site. Extravasation may cause necrosis and sloughing of surrounding tissue. Large veins of the antecubital fossa are preferred to veins in the dorsum of the hand or ankle. Less suitable infusion sites should be used only if the patient's condition requires immediate attention. The physician should switch to more suitable sites as rapidly as possible. The infusion site should be continuously monitored for free flow.

Occlusive Vascular Disease – Patients with a history of occlusive vascular disease (for example, atherosclerosis, arterial embolism, Raynaud's disease, cold injury, diabetic endarteritis, and Buerger's disease) should be closely monitored for any changes in color or temperature of the skin in the extremities. If a change in skin color or temperature occurs and is thought to be the result of compromised circulation to the extremities, the benefits of continued INTROPIN infusion should be weighed against the risk of possible necrosis. This condition may be reversed by either decreasing or discontinuing the rate of infusion.

IMPORTANT – Antidote for Peripheral Ischemia: To prevent sloughing and necrosis in ischemic areas, the area should be infiltrated as soon as possible with 10 to 15 ml. of Saline solution containing from 5 to 10 mg. of Regitine® (brand of phentolamine), an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, and the solution liberally infiltrated throughout the ischemic area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, phentolamine should be given as soon as possible after the extravasation is noted.

Avoid Cyclopropane or Halogenated Hydrocarbon Anesthetics – Cyclopropane or halogenated hydrocarbon anesthetics increase cardiac autonomic irritability and therefore may sensitize the myocardium to the action of certain intravenously administered catecholamines. This interaction appears to be related both to pressor activity and to beta adrenergic stimulating properties of these catecholamines. Therefore, as with certain other catecholamines, and because of the theoretical arrhythmogenic potential, INTROPIN should be used with EXTREME CAUTION in patients inhaling cyclopropane or halogenated hydrocarbon anesthetics.

Careful Monitoring Required – Close monitoring of the following indices – urine flow, cardiac output and blood pressure – during INTROPIN infusion is necessary as in the case of any adrenergic agent.

ADVERSE REACTIONS: The most frequent adverse reactions observed in clinical evaluation of INTROPIN included ectopic beats, nausea, vomiting, tachycardia, anginal pain, palpitation, dyspnea, headache, hypotension, and vasoconstriction. Other adverse reactions which have been reported infrequently were aberrant conduction, bradycardia, piloerection, widened QRS complex, azotemia, and elevated blood pressure.

DOSAGE AND ADMINISTRATION:

WARNING: This is a potent drug: It must be diluted before administration to patient.

Suggested Dilution – Transfer contents of one ampul (5 ml. containing 200 mg. INTROPIN) by aseptic technique to either a 250 ml. or 500 ml. bottle of one of the following sterile intravenous solutions:

1) Sodium Chloride Injection, USP
2) Dextrose 5% Injection, USP
3) Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
4) 5% Dextrose in 0.45% Sodium Chloride Solution
5) Dextrose (5%) in Lactated Ringer's Solution
6) Sodium Lactate (1/6 Molar) Injection, USP
7) Lactated Ringer's Injection, USP

These dilutions will yield a final concentration for administration as follows:
250 ml. dilution contains 800 mcg./ml. of INTROPIN
500 ml. dilution contains 400 mcg./ml. of INTROPIN

INTROPIN has been found to be stable for a minimum of 24 hours after dilution in the sterile intravenous solutions listed above. However, as with all intravenous admixtures, dilution should be made just prior to administration.

Do **NOT** add INTROPIN Injection to 5% Sodium Bicarbonate or other alkaline intravenous solutions, since the drug is inactivated in alkaline solution.

Rate of Administration – INTROPIN, after dilution, is administered intravenously through a suitable intravenous catheter or needle. An i.v. drip chamber or other suitable metering device is essential for controlling the rate of flow in drops/minute. Each patient must be individually titrated to the desired hemodynamic and/or renal response with INTROPIN. In titrating to the desired increase in systolic blood pressure, the optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the hemodynamic condition is stabilized.

Administration at rates greater than 50 mcg./kg./min. have safely been used in advanced circulatory decompensation states. If unnecessary fluid expansion is of concern, adjustment of drug concentration may be preferred over increasing the flow rate of a less concentrated dilution.

Suggested Regimen:

1. When appropriate, increase blood volume with whole blood or plasma until central venous pressure is 10 to 15 cm H_2O or pulmonary wedge pressure is 14-18 mm Hg.
2. Begin administration of diluted solution at doses of 2-5 mcg./kg./minute INTROPIN in patients who are likely to respond to modest increments of heart force and renal perfusion.

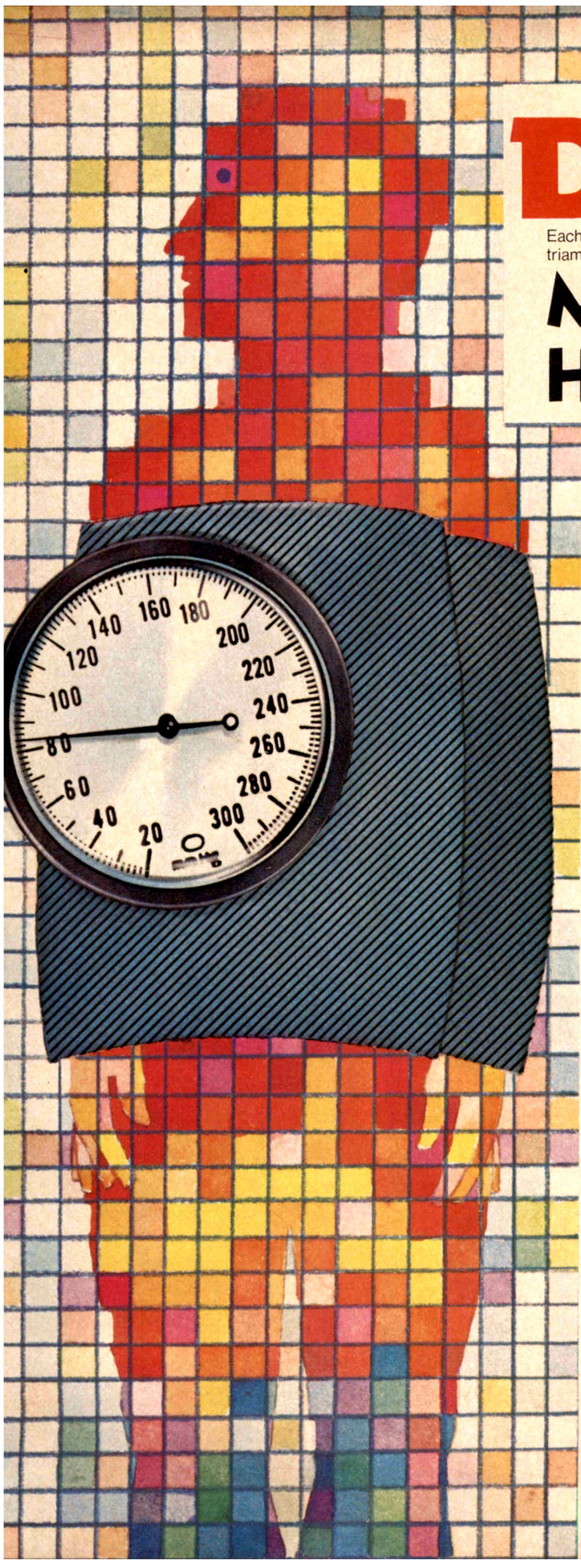
In more seriously ill patients, begin administration of diluted solution at doses of 5 mcg./kg./minute INTROPIN and increase gradually using 5 to 10 mcg./kg./minute increments up to 20 to 50 mcg./kg./minute as needed. If doses of INTROPIN in excess of 50 mcg./kg./minute are required, it is suggested that urine output be checked frequently. Should urine flow begin to decrease in the absence of hypotension, reduction of INTROPIN dosage should be considered. Multiclinic trials have shown that more than 50% of the patients were satisfactorily maintained on doses of INTROPIN less than 20 mcg./kg./minute. In patients who do not respond to these doses with adequate arterial pressures or urine flow, additional increments of INTROPIN may be employed in an effort to produce an appropriate arterial pressure and central perfusion.

3. Treatment of all patients requires constant evaluation of therapy in terms of the blood volume, augmentation of myocardial contractility, and distribution of peripheral perfusion. Dosage of INTROPIN should be adjusted according to the patient's response, with particular attention to diminution of established urine flow rate, increasing tachycardia or development of new dysrhythmias as indices for decreasing or temporarily suspending the dosage.
4. As with all potent intravenously administered drugs, care should be taken to control the rate of administration so as to avoid inadvertent administration of a bolus of drug.

OVERDOSAGE: In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce rate of administration or temporarily discontinue INTROPIN until patient's condition stabilizes. Since INTROPIN's duration of action is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha adrenergic blocking agent, phentolamine, should be considered.

HOW SUPPLIED: 5 ml. ampuls containing 40 mg. dopamine HCl per milliliter. September, 1975

ARNAR-STONE LABORATORIES, INC.
Mount Prospect, Illinois 60056
A Subsidiary of American Hospital Supply Corporation



Dyazide®

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

Makes Sense in Hypertension*

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. A brief summary follows:

* **Warning**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K+ frequently; both can cause K+ retention and elevated serum K+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

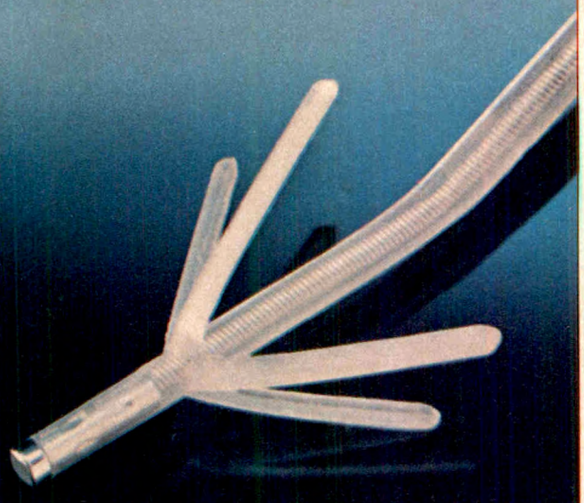
Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

SK&F CO.
a SmithKline company
Carolina, P.R. 00630

An Endocardial Tined Ventricular Lead.

The Medtronic® 6950 and 6951 unipolar and bipolar tined leads feature four integral silicone rubber tines that protrude from the lead body just proximal to the tip electrode. These tines were designed to provide better acute lead stability and reduce chronic lead dislodgement by latching onto the papillary musculature or the trabeculae of the right ventricle. The large surface area provided by the tines should also enhance the stability afforded by fibrosis.



A Small, Durable Endocardial Tined Lead.

The newest members of the Tenax™ family of self-anchoring leads – the 6961 and 6962 unipolar and bipolar leads – feature shorter, smaller tines and small tip diameter (8 French; approximately 10 French with tines folded) enabling the physician to use the more common cephalic approach. Though small, the soft, pliable tines are still long enough to become securely anchored in one or more of the interstitial spaces formed by the trabeculae of the right ventricular chamber. The lead's ring-tipped electrode provides optimum energy to the heart with improved sensing and current drain characteristics. Its durable, space-wound multifilar conductor is designed to provide a longer flex life to match the potential long effective service life of lithium powered pulse generators.

TOUGH & TENACIOUS

The TENAX™ Family of Self-Anchoring Leads from Medtronic.

Our entire family of Medtronic Tenax™ leads has one common trait:
Tenacious, positive-anchoring lead tips.
Tips designed to minimize dislodgement problems associated with standard endocardial pacing leads.
Tips that stay where you put them.

MEDTRONIC IMPLANTABLE PACING LEADS

Intended Use

Medtronic implantable pacing leads are designed to be used with Medtronic pulse generators as part of a cardiac pacing system (see product labeling for specific directions regarding applications).

Contraindications

Endocardial pacing leads are contraindicated in the presence of tricuspid valvular disease.

Myocardial leads are contraindicated for a patient whose myocardium is thin-walled, suffused with fat, or infarcted in the area of electrode placement.

Myocardial leads may be contraindicated in the older high risk patients with a low tolerance to general anesthesia.

Atrial J-leads are contraindicated in the absence of a right atrial appendage.

Warnings

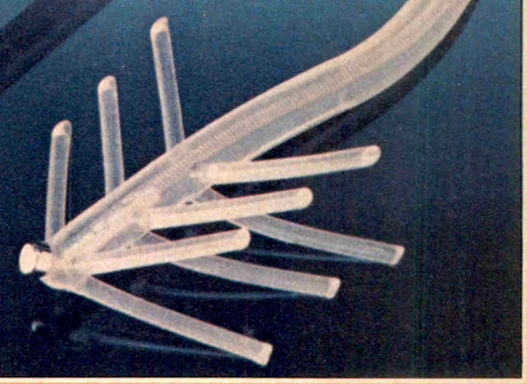
An implanted lead constitutes a direct, low resistance current path to the myocardium.

A Unique Sutureless Myocardial Lead.

Our Model 6917 sutureless lead is the largest selling pacing lead worldwide. Its unique screw-in electrode, introduced in 1973, eliminates the necessity of making a stab wound and suturing to the myocardium. The electrode tip is secured by simply rotating it into the myocardium. The 6917A has been successfully installed on either the right or left ventricle using a variety of surgical approaches such as limited thoracotomy, subxiphoid, transxiphoid, and transmediastinal, in some cases using only local anesthesia.

A Tined Endocardial Atrial J-Shaped Lead.

The Medtronic 6991 unipolar and 6990 bipolar leads are molded into a J configuration to facilitate placement and lodging into the right atrial appendage. During insertion, the J tip is straightened by means of lead stylets. The distal end of the J contains a series of nine silicone rubber tines; the electrode tip is canted inward so the force exerted by the tines will enable the electrode to contact the endocardial surface of the atrium. After the lead tip has been advanced into the desired position, the stylets are partially withdrawn to allow the lead to assume its natural J shape. The tines are fixed into the atrial appendage by becoming anchored in one or more of the interstitial spaces formed by trabeculae.



For further information on the Medtronic Tenax™ lead family, contact your Medtronic, Inc. representative or write for a complete technical brochure.

Medtronic, Inc.
3055 Old Highway Eight, P.O. Box 1453
Minneapolis, Minnesota 55440

Medtronic

Helping You Help
The Pacemaker Patient

uring the connection and testing procedures, only battery-powered pulse generators ould be used with the lead system to protect against ventricular fibrillation induced by ernating current leakage. Extreme caution must be taken to properly ground all e-powered equipment used in the vicinity of the patient.

ecautions

e pacing system may cease to function due to lead-related problems such as splacement, fracture, fibrotic tissue formation and elevated thresholds.

Side Effects

Body rejection phenomena, infection, erosion or migration through body tissue, transvenous lead-related thrombosis, embolism.

How Supplied

Medtronic permanent implantable leads are supplied sterilized and individually wrapped. Medtronic pacing leads are designed to be used with Medtronic pulse generators.

A reminder

LANOXIN®
(digoxin)

0.125 mg
yellow
imprinted

0.25 mg
white
imprinted & scored

0.5 mg
green
imprinted & scored

Complete literature available on request from Professional Services Dept. PML

Wellcome

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North Carolina 27709

SEPTEMBER 1978

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CLINICAL STUDIES

Myocardial Imaging With Thallium-201: A Multicenter Study in Patients With Angina Pectoris or Acute Myocardial Infarction

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A multicenter study of rest and exercise thallium-201 myocardial imaging in 190 patients from five centers was performed. Exercise images were obtained after graded treadmill or bicycle stress with use of five different gamma camera models and were interpreted by the originating investigator without knowledge of other clinical data. Of 42 patients with less than 50 percent coronary stenosis, 4 (10 percent) had a resting image defect, 1 (2 percent) a new exercise defect and 5 (12 percent) either a resting or an exercise image defect, or both. Of 148 patients with coronary stenosis of 50 percent or greater, 64 (45 percent) had an image defect in the study at rest, 90 (61 percent) had new or increased defects after exercise, and 115 (78 percent) had resting or exercise defects, or both. New exercise image defects were more common than exercise S-T depression (90 of 148 [61 percent] versus 62 of 148 [42 percent]; $P < 0.01$). In a second group of 111 patients with acute myocardial infarction studied at three centers, 90 patients (81 percent) had image defects compared with 71 (64 percent) who had new electrocardiographic Q waves ($P < 0.01$). Smaller infarctions, as assessed with serum enzyme values, and diaphragmatic infarctions were less commonly detected than larger or anterior infarctions. These findings suggest that myocardial imaging complements the electrocardiographic identification of acute myocardial infarction or exercise-induced myocardial ischemia.

Myocardial imaging at rest and during stress may detect regional myocardial infarction or ischemia.[1–5] Previous reports from selected institutions have dealt with small groups of patients and patient populations peculiar to the reporting institutions. The present cooperative study, employing thallium-201, was undertaken to define the clinical utility of myocardial perfusion imaging in a large series of patients from five medical institutions.* The specific aims were to evaluate (1) the sensitivity and specificity of imaging at rest and during exercise in detecting coronary artery disease; (2) the sensitivity of myocardial imaging at rest

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*Participating institutions were the Johns Hopkins University School of Medicine (47 patients), Yale University School of Medicine (69 patients), University of California at Davis School of Medicine (31 patients), University of California at San Diego School of Medicine (87 patients) and the Seattle Veterans Administration Hospital (101 patients).

in detecting acute myocardial infarction; and (3) the uniformity of the results derived from data obtained at the five centers with several types of scintillation cameras, different physicians and technical staff and variable patient populations.

Material and Methods

Patient selection: *Stable angina:* Between October 1975 and December 1976, 195 patients with chronic stable angina due to suspected or proved coronary artery disease were enrolled for study with thallium-201 myocardial imaging at rest and during exercise. No patient had sustained a myocardial infarction in the preceding 2 months and no patient had unstable angina. Patients in five institutions were selected from those undergoing diagnostic cardiac catheterization for coronary artery disease. Criteria for selection were a technically satisfactory coronary arteriogram plus patient and isotope availability for the resting and exercise studies. From an original group of 195 patients, 2 had technically unsatisfactory thallium-201 images, 2 had associated nonatherosclerotic heart disease and 1 had a technically unsatisfactory coronary angiogram (right coronary artery not studied). With exclusion of these 5 patients, the study population consisted of 190 patients, including 5 patients with normal myocardial images after exercise who underwent no study at rest. These patients were assumed to have normal resting images.

Acute myocardial infarction: One hundred forty-five patients from three institutions had a single thallium-201 image performed at rest after hospital admission for proved acute myocardial infarction. Only 111 of these patients were included in the study because the other 34 had a history of prior myocardial infarction. The patients were considered to have had an acute myocardial infarction if two or more of the following criteria were present: (1) clinical syndrome of severe substernal pain of more than 15 minutes' duration that did not respond to nitroglycerin, (2) new 0.04 second electrocardiographic Q waves representing 25 percent or more of the height of the R wave, or (3) elevation of serum creatine kinase to more than twice the control value. Patients were studied only after stabilization of complications such as shock or arrhythmias and on an average of 5.4 days (range 1 to 34 days) after the onset of infarction. Imaging was performed in the coronary care unit in most instances.

All patients in the protocols for stable angina and acute infarction gave informed consent for the study after the experimental nature of the study and the potential risks and benefits were explained.

Imaging: Myocardial imaging was performed using standard scintillation cameras: Ohio-Nuclear Series 100 (146 cases, 43 percent), Baird Atomic System 70 (69 cases, 20 percent), Searle Pho Gamma IV (104 cases, 31 percent), Searle Pho Gamma II (14 cases, 4 percent) and Picker Dyna-Mo (portable) (2 cases, 1 percent). High resolution collimation was used in 286 cases (85 percent), and converging collimation in 49 cases (15 percent). An energy window of 20 to 25 percent centered about the 80 kev mercury X rays was employed. For resting studies, 1.5 to 2.0 millicuries (mCi) of thallium-201 (New England Nuclear Corp., North Billerica, Massachusetts) was injected intravenously with the patient standing (group with angina) or supine (group with acute infarction). Most patients were studied after a 2 to 4 hour fast to minimize gastrointestinal uptake of thallium-201. Imaging was started 10 to 15 minutes after injection. Polaroid® scintiphotographs, with a count of 300,000 to 400,000, were obtained in the anterior, 45° left anterior oblique and left lateral views. For the exercise study, the imaging procedure was identical except that the isotope was injected 30 to 60 seconds before the termination of exercise. Image interpretations were made from either the original unprocessed scintiphotograph or from scintiphotographs with 20 to 25 percent background subtraction. All images were interpreted by the originating investigator without knowledge of the clinical findings or the patient's identification.

Images were graded as normal or abnormal, and the location of the image defect was localized as anterior (anteromedial wedge in the left anterior oblique view), inferior (inferior wedge in the left anterior oblique view), posterior (posterolateral wedge of activity in the left anterior oblique view) or apical (the tip of the ventricle in the anterior or the left lateral view).[6] A defect was considered present if a discrete region of absent or decreased activity (estimated visually as a reduction of at least 50 percent) was present. Only a new defect or a defect in addition to or larger than that present at rest was considered exercise-induced. Patients with a defect at rest that remained unchanged after exercise were considered to have only a resting defect.

Exercise electrocardiography: Patients underwent exercise with use of the Bruce[7] graded treadmill protocol to symptom-limited maximum in three institutions (142 patients) or with use of a bicycle ergometer in two institutions (48 patients). In the latter patients, exercise was initiated at a work load of 150 kilopond-meters/min and advanced 150 kilopond-meters/min every 3 minutes until the symptomatic limit or 85 percent of predicted heart rate was achieved. A modified V_5 electrode was monitored throughout and after exercise and the S-T segment response was considered positive if flat or downsloping S-T depression of 1 mm or more occurred. Duration of treadmill or bicycle exercise was expressed as functional aerobic impairment.[7]*

Coronary angiography: This was performed with either the Judkins or Sones technique, and the percent luminal narrowing of vessel diameter was estimated. Angiograms were reviewed and graded by two independent observers, and in cases of disagreement a consensus reached. Angiography was performed within 3 weeks of the thallium-201 study. Stenoses of 50 percent or greater were considered to represent significant coronary artery disease.

Institutional comparisons: The mean age of patients in the rest/exercise protocol (50 ± 9 years [±1 standard deviation]) and the acute myocardial infarction protocol (58 ± 12 years) did not differ significantly among institutions (Student's *t* test). In the rest/exercise study, a greater proportion of patients from one institution had hemodynamically significant coronary artery disease (98 versus 71 percent at remaining institutions). However, among all patients with significant coronary artery disease (50 percent or greater diameter stenosis), the percent of those with exercise S-T depression, electrocardiographic Q waves and one, two or three vessel coronary artery disease did not differ significantly among institutions. Similarly, for patients with acute myocardial infarction, there were no significant differences among the three hospitals in the percent of patients with electrocardiographic Q waves or in average time of imaging after myocardial infarction.

* Functional aerobic impairment is defined as (predicted maximal oxygen intake-observed oxygen intake/predicted maximal oxygen intake × 100) corrected for age, sex and chronic activity level; derived by nomogram from treadmill data and for bicycle data from estimated oxygen consumption.[8] Mean functional aerobic impairment for the entire group was 33 percent (range −28 to +85 percent). Functional aerobic impairment for patients who exercised on the bicycle was greater (52 ± 15 percent [±1 standard deviation]) than on the treadmill (27 ± 27 percent) ($P < 0.01$; Student's *t* test).

Results

Rest/Exercise Studies

One hundred forty-eight patients had angiographic coronary artery disease (diameter stenosis of 50 percent or greater), and 42 patients had no or insignificant coronary artery disease (less than 50 percent diameter stenosis). Complete electrocardiographic, image and exercise data for all 190 patients are illustrated in Figure 1.

Patients without significant coronary artery disease: Of the 42 patients with no or insignificant coronary artery disease (less than 50 percent diameter stenosis), 1 patient (2 percent) had an exercise image defect and 4 (10 percent) had defects in the resting image (Fig. 1). Five patients had exercise S-T depression (5 of 42; 12 percent) and 1 (2 percent) had an electrocardiographic Q wave. The proportion of patients with a thallium-201 image abnormality after exercise or at rest (5 of 42; 12 percent) was not significantly different from the proportion of patients with exercise S-T depression alone or electrocardiographic Q waves, or both (6 of 42; 14 percent).

Patients with coronary artery disease: Sixteen of the 148 patients with coronary artery disease had either digitalis effect (11 patients) or left bundle branch block (5 patients) that prevented identification of S-T segment depression. Of the 132 patients whose S-T segment could be analyzed, 62 (47 percent) had S-T depression and 77 (58.3 percent) had new or enlarged exercise thallium-201 image defects (Fig. 2). The larger proportion of patients with exercise thallium-201 defects approached statistical significance at the $P = 0.068$ level (McNemar test of correlated proportions). If the patients with uninterpretable S-T changes are considered as having negative findings or no S-T depression, then 62 patients (42 percent) had exercise S-T depression and 90 (61 percent) had new exercise thallium-201 defects ($P < 0.01$). Thirteen of the 16 patients (81 percent) with an uninterpretable S-T segment had exercise thallium-201 defects. Among the 132 patients with an interpretable S-T response, 99 (75 percent) had either exercise S-T depression or an exercise thallium-201 image defect, or both, compared with 62 (47 percent) who had only S-T depression ($P < 0.01$) (Fig. 3). The interrelation between exercise S-T depression and ex-

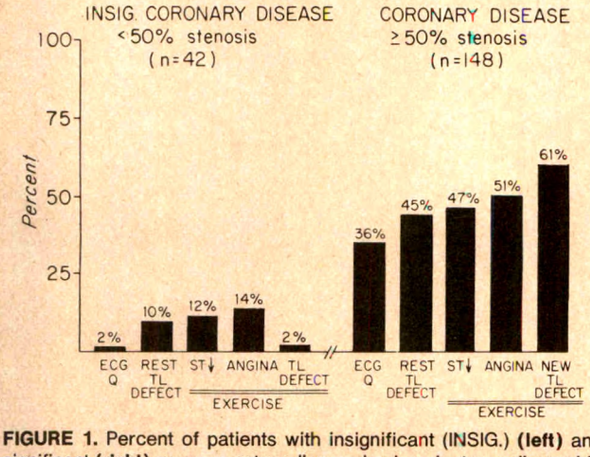

FIGURE 1. Percent of patients with insignificant (INSIG.) **(left)** and significant **(right)** coronary artery disease having electrocardiographic (ECG) Q waves, defects in the resting thallium-201 (TL) image, exertional S-T segment depression (ST↓), exertional angina (during treadmill exercise) and a new thallium-201 image defect after exertion. The 47 percent with exercise S-T depression excludes 16 patients with an uninterpretable S-T response (see text). n = number of patients.

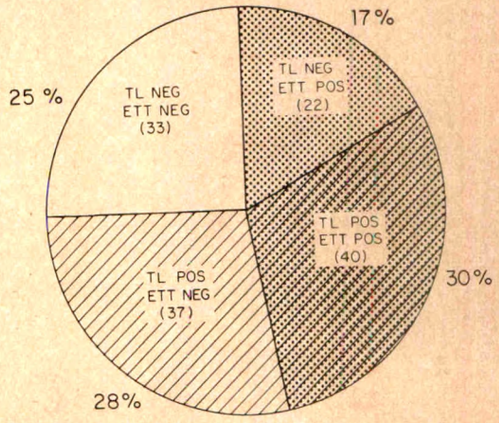

FIGURE 2. Comparison of exercise-induced electrocardiographic (ECG) S-T segment depression and new exercise-induced thallium-201 (TL) image defects in 132 patients with significant coronary artery disease. Sixteen patients with an uninterpretable exercise S-T response are excluded. Thirty-three patients (25 percent) had neither exercise-induced S-T segment depression (ETT NEG) nor thallium-201 defects; 22 patients (17 percent) had exercise S-T segment depression (ETT POS) and no exercise thallium-201 defect; 40 patients (30 percent) had both exercise S-T depression and an exercise thallium-201 defect; and 37 patients (28 percent) had exercise thallium-201 defects with no exercise S-T depression.

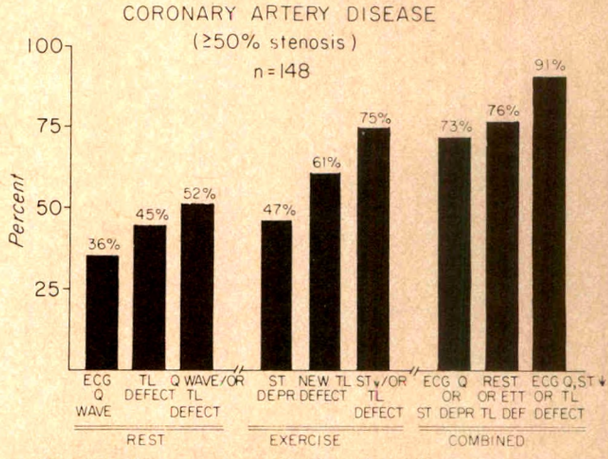

FIGURE 3. Left bars, percent of 148 patients with significant coronary artery disease having electrocardiographic (ECG) Q waves or a thallium-201 (TL) defect, or either, at rest; **center bars,** percent having exercise S-T depression (ST DEPR; ST↓), exercise thallium-201 defects, or either; **right bars,** percent having either an electrocardiographic abnormality (Q wave or exercise S-T depression), rest/exercise thallium-201 defects (ETT TL DEF.), or any combination thereof. Only those 132 patients with an interpretable exercise response are included in the columns showing exercise S-T depression (see text).

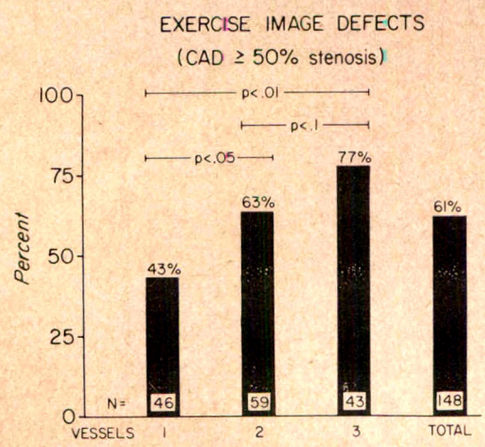

FIGURE 4. Patients with significant two or three vessel coronary artery disease (CAD) were more apt to have exercise image defects than those with single vessel disease. p = probability.

ercise-induced image abnormalities for these 132 patients is illustrated in Figures 2 and 3, which show graphically that exercise imaging and exercise electrocardiography were complementary and not simply positive in the same cohort of patients.

The presence of electrocardiographic Q waves, any electrocardiographic abnormality, exercise-induced angina or exercise S-T depression was not significantly related to the development of an exercise perfusion image. The duration of exercise had an inverse correlation with the presence of exercise image defects; the mean functional aerobic impairment for patients without defects was 26.7 ± 27 versus 40.7 ± 24 percent (P <0.01) for those with defects (that is, patients with exercise defects exercised less than those without defects). The proportion of patients with two vessel (37 of 59; 63 percent) or three vessel disease (33 of 43; 77 percent) who had exercise image defects was greater than that of patients with single vessel disease (20 of 46; 43 percent, P <0.05, chi square test) (Fig. 4).

Sensitivity of imaging versus electrocardiogram: Overall, 120 of 132 patients (91 percent) with coronary artery disease were identified either by imaging or the electrocardiogram, or both, when the resting and exercise studies were combined. This proportion was significantly greater than that for electrocardiographic changes alone (exercise S-T depression or electrocardiographic Q waves [97 of 132; 73 percent, P <0.001]) or for thallium-201 image abnormalities alone (resting or exercise [100 of 132; 76 percent, P <0.001]). Thus, the diagnostic sensitivity of rest/exercise thallium-201 imaging, when combined with rest/exercise electrocardiography, was greater than that achieved with either study alone. Additionally in this study, 8 of 42 patients (19 percent) without coronary artery disease had either rest/exercise thallium-201 defects or rest/exercise electrocardiographic changes, or both (specificity rate 81 percent); this did not differ significantly from the percent with rest/exercise thallium-201 defects alone (5 of 42; 12 percent, specificity rate 88 percent), or rest/exercise electrocardiographic changes alone (6 of 42; 14 percent, specificity rate 86 percent). The sensitivity for detecting coronary artery disease was thus enhanced by combining the imaging and electrocardiographic responses without a significant sacrifice in specificity.

Comparison of results among five institutions: The percent of patients having either rest or exercise thallium-201 image defects was not significantly different among various institutions (chi square test). This was true for patients with significant coronary artery disease and for those without. Table I illustrates these findings, by institution, for new exercise-induced image defects both for the 42 patients without significant coronary artery disease and for the 148 patients with disease. Table II shows the data for resting image defects. No results in the rest/exercise protocol were modified when the criterion of 70 percent rather than 50 percent diameter stenosis was used for inclusion in the group with "significant coronary artery disease"; only 5 of 148 patients (3 percent) had isolated disease of 50 percent or greater but less than 70 percent diameter stenosis.

Acute Myocardial Infarction

Of the 145 patients with acute myocardial infarction who had thallium-201 images, 123 (85 percent) had image defects and 22 (15 percent) did not. Because

TABLE I

Institutions and the Number of Patients With New Exercise-Induced Thallium-201 Defects*

	Institution				
	1	2	3	4	5
Patients with coronary artery disease					
Image defect	28	50	9	3	0
No defect	18	26	12	2	0
Patients without coronary artery disease					
Image defect	0	1	0	0	0
No defect	1	24	5	10	1

*There were no significant differences (chi square test) among institutions in sensitivity or specificity in disease detection with the exercise thallium–201 study.

TABLE II

Institutions and the Number of Patients With Thallium-201 Defects in the Image at Rest*

	Institution				
	1	2	3	4	5
Patients with coronary artery disease					
Image defect	26	28	11	2	0
No defect	20	48	10	3	0
Patients without coronary artery disease					
Image defect	0	1	1	2	0
No defect	1	24	4	8	1

*There were no significant differences (chi square test) among institutions in sensitivity or specificity in disease detection with the resting thallium-201 image.

thallium-201 imaging cannot distinguish between new and old myocardial infarction, 34 patients with a history of prior myocardial infarction were excluded from further analysis. Of the remaining 111 patients, 90 (81 percent) had thallium-201 image defects and 21 (19 percent) did not. The percent of patients with a new image defect did not differ significantly among the three institutions enrolling patients with acute infarction.

Time of imaging: Patients with suspected acute myocardial infarction had imaging performed 1 to 34 days (mean 5.4 days) from the onset of infarction. Patients with image abnormalities were studied an average of 4.6 days compared with 8.7 days for those without image defects ($P < 0.09$). The percent of patients with image defects studied 7 or more days after acute infarction was lower (17 of 24; 70 percent) than that of those studied earlier (73 of 86; 85 percent) but the difference did not reach statistical significance ($0.1 < P < 0.25$). There were similarly no significant differences in the rates of detection of infarction among patients studied in the following time intervals after infarction: 0 to 12 hours, 12 to 24 hours, 24 to 72 hours, 72 hours to 1 week and more than 1 week. However, only 9 patients were studied within the first 24 hours.

Presence and location of electrocardiographic Q waves: Among the 111 patients without evidence for prior myocardial infarction, 71 (64 percent) had new electrocardiographic Q waves and a greater proportion (90; 81 percent) had thallium-201 image defects ($P < 0.01$). As a group, 102 of the 111 patients (92 percent) had either an electrocardiographic Q wave or a thallium-201 image defect, or both. The rate of detection by thallium-201 imaging did not differ between patients with and without new electrocardiographic Q waves (59 of 71; 83 percent versus 31 of 40; 78 percent). In the group without electrocardiographic Q waves (nontransmural myocardial infarction), the location of the infarction could be ascertained from the image studies (Table III).

The electrocardiographic location of the infarction did modify the extent to which imaging was positive. More patients with an electrocardiographically anterior myocardial infarction (39 of 41; 95 percent) than with an inferior myocardial infarction (27 of 37; 73 percent, $P < 0.02$) were detected with imaging. There were too few patients with a lateral (seven patients) or a posterior (one patient) infarction for statistical analysis, although all had image defects. The anatomic localization of defects with the two techniques was generally concordant. All patients with posterior or lateral electrocardiographic Q waves, or both, had image defects in these locations. Twenty-three of 27 patients (85 percent) with diaphragmatic electrocardiographic Q waves had inferior image defects; the remainder had posterolateral image defects. Thirty-four of 39 patients (87 percent) with anterior electrocardiographic Q waves had anterior image defects; the remainder had inferior defects. Apical defects occurred in combination with some other defects and were of no localizing value as such. Six patients with nontransmural myocardial infarction had isolated apical defects (Table III).

TABLE III

Location of Image Defects in 31 Patients With Nontransmural Myocardial Infarction

Site	Patients (no.)	Site	Patients (no.)
Anterior	10	Anteroapical	3
Posterior	2	Inferoposterior	1
Inferior	6	Apical-posterior	1
Apical	6	Inferoapical	2

Enzyme data: Only one third (3 of 9; 33 percent) of patients studied with peak serum creatine kinase values between two and three times normal had image defects. A larger proportion (87 of 101; 86 percent, $P < 0.001$) of those with creatine kinase values three or more times normal had image defects.

Discussion

This study was performed to test the general efficacy of thallium-201 myocardial imaging in detecting ischemic heart disease. The results demonstrate that for bicycle and treadmill exercise, thallium-201 imaging at rest and during exercise complemented the role of rest/exercise electrocardiography in the identification of coronary artery disease. This was true for a broad spectrum of institutions, image interpreters and gamma cameras. The combination of rest/exercise thallium-201 and rest/exercise electrocardiography detected coronary disease in 91 percent of all patients with angiographically documented coronary artery disease.

False positive studies: Because most of the false positive imaging studies occurred in patients with false positive electrocardiographic results, the specificity of the combined procedures was not different from that of electrocardiography alone in this series. The definition of coronary artery disease employed (50 percent or greater diameter stenosis) artifactually reduced the reported specificity in one case. This patient was considered to have a false positive image because he had no coronary stenosis of 50 percent or greater. He had had a prior myocardial infarction documented with serum enzymes and electrocardiographic Q waves and had only a resting defect on imaging. Thus, an old infarction was correctly identified. A second patient with normal coronary arteries considered to have a false positive imaging study had a defect in the resting image that was considered to have normalized in the study performed during exercise. This was the only case of such apparent resolution of a resting perfusion defect with exercise. Although the resting image was considered abnormal at the time it was obtained, the normalcy of the exercise image, which is typically of higher overall quality, suggests that the resting study was misinterpreted. Of the remaining three patients with a false positive study, two patients had defects in the resting image that persisted in the exercise image and one patient with a normal resting study had a defect on exercise; these three cases thus represent definite false positive studies. In one of these patients an inferior defect developed

with exercise in association with exercise angina and S-T depression. This patient had normal coronary arteries although catheter-induced spasm of the right coronary artery occurred on angiography. The second patient had an isolated 40 percent stenosis of the distal left anterior descending coronary artery, an inferior defect at rest and during exercise and no exercise angina or S-T depression. The third patient had an anterior defect at rest and during exercise, normal coronary arteries and both angina and S-T depression on exercise. Although imaging in these patients yielded false positive results when compared with the arteriographic findings, it is possible that imaging identified regional perfusion abnormalities not identified with the arteriogram.

Sensitivity of imaging in ischemia and infarction: Among patients with coronary artery disease, imaging showed a decreased sensitivity in detecting ischemia only in patients with single vessel disease. It thus appears that relatively more patients with two and three vessel (potentially more lethal) disease[9,10] will be detected with imaging. Rest/exercise thallium-201 imaging was particularly useful in patients in whom either digitalis effect or the presence of left bundle branch block made S-T segment interpretation impossible; 13 of 16 patients in this group had thallium-201 defects on exercise. Additionally, imaging allowed geographic localization of the site of ischemia. Such localization may be of value in prognosis,[11] in planning for coronary bypass surgery or in serial studies.

In our study the thallium-201 image was more sensitive than electrocardiographic Q waves as a detector of acute myocardial infarction. Additionally, among those 40 patients with nontransmural myocardial infarction, image defects were found in 78 percent, allowing anatomic localization (Table III). Patients having more than three times the control value of serum creatine kinase were more apt to have abnormal images. These results support the findings of others[12,13] that thallium-201 imaging is a sensitive indicator of acute myocardial infarction and documents that patients with smaller infarcts as assessed with serum enzyme values are less apt to have abnormal images than those with larger infarcts. The failure to detect small myocardial infarcts is in keeping with previous experimental data[14,15] showing that a minimal mass of real or simulated infarction is required for external detection.

We conclude that myocardial imaging with thallium-201 complements electrocardiography in the identification of acute myocardial infarction or exercise-induced myocardial ischemia. The geographic location of ischemia as well as an estimate of its magnitude may also be ascertained. These findings apply to a broad range of patient populations, gamma scintillation cameras and image interpreters and institutions.

References

1. **Zaret BL, Strauss HW, Martin ND, et al:** Noninvasive regional myocardial perfusion with radioactive potassium. N Engl J Med 288:809–812, 1973
2. **Martin ND, Zaret BL, McGowan RL, et al:** Rubidium-81: a new myocardial scanning agent. Radiology 111:651–656, 1974
3. **Bailey IK, Griffith LSC, Rouleau J, et al:** Thallium-201 myocardial perfusion imaging at rest and during exercise. Circulation 55: 79–87, 1977
4. **Ritchie JL, Trobaugh GB, Hamilton GW, et al:** Myocardial imaging with ^{201}thallium at rest and during exercise: comparison with coronary arteriography and resting and stress electrocardiography. Circulation 56:66–71, 1977
5. **Taradash M, Botvinick E, Shames D, et al:** T1-201 myocardial perfusion imaging for the clinical clarification of normal, abnormal, and equivocal stress tests (abstr). Circulation 54: Suppl II: II-217, 1976
6. **Ritchie JL, Hamilton GW, Williams DL, et al:** Myocardial imaging with radionuclide-labeled particles. Radiology 121:131–138, 1976
7. **Bruce RA, Kusumi F, Hosmer D:** Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J 85:546–562, 1973
8. **Astrand PO, Rodahl K:** Textbook of Work Physiology. New York, McGraw-Hill, 1970, p 619
9. **Bruschke AVG, Proudfit WL, Sones FM:** Progress study of 590 consecutive nonsurgical cases of coronary disease followed 5–9 years. I. Arterographic correlations. Circulation 47:1147–1153, 1973
10. **Hammermeister KE, DeRouen TA, Murray JA, et al:** Effect of aortocoronary saphenous vein bypass grafting on death and sudden death. Comparison of nonrandomized medically and surgically treated cohorts with comparable coronary disease and left ventricular function. Am J Cardiol 39:925–934, 1977
11. **Webster JS, Moberg C, Rincon G:** Natural history of severe proximal coronary artery disease as documented by coronary cineangiography. Am J Cardiol 33:195–200, 1974
12. **Wackers FJT, Sokole EB, Samson G, et al:** Value and limitations of Thallium-201 scintigraphy in the acute phase of myocardial infarction. N Engl J Med 295:1–5, 1976
13. **Parkey RW, Bonte FJ, Stokely EM, et al:** Acute myocardial infarction imaged with ^{99m}Tc-stannous pyrophosphate and ^{201}Tl: a clinical evaluation. J Nucl Med 17:771–779, 1976
14. **Mueller TM, Marcus ML, Ehrhardt JC, et al:** Limitations of thallium-201 myocardial perfusion scintigrams. Circulation 54: 640–646, 1976
15. **Manspeaker HF, Montgomery W, Schafer W, et al:** A comparative evaluation of imaging devices for myocardial studies using thallium-201 (abstr). J Nucl Med Tech 4:99, 1976

Exercise-Induced Left Ventricular Dysfunction in Symptomatic And Asymptomatic Patients With Aortic Regurgitation: Assessment With Radionuclide Cineangiography

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In patients with aortic regurgitation, left ventricular dysfunction at rest, which is associated with a poor long-term prognosis, often develops before severe symptoms. To determine whether evidence of left ventricular dysfunction could be detected before it appeared at rest, 43 patients with severe aortic regurgitation were studied using radionuclide cineangiography during exercise. In 30 normal subjects, left ventricular ejection fraction increased during exercise (57 ± 1 percent [mean ± standard error] at rest, 71 ± 2 percent during exercise, $P < 0.001$). In contrast, among 21 *symptomatic* patients, ejection fraction was normal at rest in 14 patients (average 47 ± 2 percent) but normal during exercise in only one patient (average 38 ± 2 percent, $P < 0.001$). Ejection fraction was normal at rest in 21 of 22 *asymptomatic* patients (average 62 ± 2 percent) but was normal during exercise in only 13 (average 57 ± 3 percent, $P < 0.001$). Thus, exercise-induced left ventricular dysfunction can precede symptoms and dysfunction at rest. Radionuclide assessment of left ventricular function during exercise may prove valuable in sequentially following the state of left ventricular function in patients before the onset of symptoms or of irreversible left ventricular failure.

Although in symptomatic patients with severe aortic regurgitation various measures of left ventricular function, including ejection fraction, end-diastolic pressure and cardiac output, may be normal when measured at rest, dysfunction almost invariably develops during exercise or other stress.[1,2] Even asymptomatic patients, who usually exhibit normal left ventricular function at rest, may manifest functional abnormalities when the heart is subjected to stress.[2]

Recently we demonstrated that noninvasive radionuclide cineangiography performed during exercise can detect abnormalities of left ventricular function not apparent at rest in patients with coronary artery disease.[3,4] In this investigation, we conducted radionuclide cineangiographic studies during exercise in patients with aortic regurgitation in the hope of finding evidence of deterioration of left ventricular function before the development of symptoms or the occurrence of left ventricular dysfunction at rest.

Methods

Patients

All patients with severe aortic regurgitation seen at the National Heart, Lung, and Blood Institute between April 1976 and June 1977 were studied. The group consisted of 37 men and 6 women, 16 to 65 years of age. In all 21 symptomatic patients and in 14 of the 22 asymptomatic patients, severe aortic regurgitation was documented with aortic root contrast cineangiography performed within 2 days of radionuclide cineangiography. In four other asymptomatic patients, the diagnosis of severe aortic regurgitation had been documented with catheterization studies performed 1 or more years before the present study.

Grading of aortic regurgitation: Severe aortic regurgitation was defined as dense opacification of the left ventricle, equal to or greater than aortic opac-

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ification, occurring within two beats after the injection of contrast medium into the aortic root and with clearing of contrast medium from the left ventricle delayed for more than three beats after cessation of injection. In addition, all patients had left ventricular dilatation with echocardiographic left ventricular transverse dimension in diastole ($LVTD_d$) greater than 60 mm or left ventricular end-diastolic volume greater than 200 ml as assessed with contrast left ventriculography. In the four asymptomatic patients who did not undergo catheterization, evidence of severe aortic regurgitation included (1) a holodiastolic aortic regurgitant murmur of at least grade 3/6; (2) systemic arterial diastolic pressure of 50 mm Hg or less measured with arm cuff sphygmomanometry, with a pulse pressure of 80 mm Hg or greater; (3) evidence of left ventricular dilatation on echocardiography (transverse dimension greater than 60 mm); and (4) no evidence of mitral regurgitation (on auscultation) or stenosis (on echocardiography).

Functional status: For purposes of this analysis, patients were considered asymptomatic only if they had no history of symptoms of congestive heart failure, chest pain, lightheadedness or exercise intolerance; thus, such subjects functionally were in New York Heart Association class I.[5] All other patients had symptoms consisting of one or more of the following: moderately severe dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, angina, syncope or presyncope. In this hospital any one of these symptoms is considered an indication for operation in a patient with severe aortic regurgitation. Three additional patients were considered symptomatic although their symptoms were judged to be sufficiently mild or atypical (for example, nonreproducible mild exercise intolerance or nonexertional chest pain) to require no operation.

In patients taking digitalis or diuretic drugs, these medications were discontinued approximately 1 week before the study. No patient was taking propranolol, and one symptomatic patient was taking quinidine, 200 mg four times daily, at the time of study.

Cardiac catheterization: In addition to aortic root cineangiography, intracardiac pressure recordings were obtained and contrast left ventriculograms were performed in the right anterior oblique projection. Patients were excluded from analysis if at catheterization they manifested a systolic gradient greater than 10 mm Hg across the aortic valve, an end-diastolic gradient across the mitral valve or systolic mitral regurgitation. In the four asymptomatic patients who underwent catheterization more than 1 year earlier, left ventricular end-diastolic pressure was not tabulated for this analysis. All symptomatic patients over 30 years of age underwent coronary arteriography. Patients were excluded from analysis if coronary arterial narrowing of 30 percent or greater was noted.

M mode echocardiography was performed in each patient for determination of left ventricular transverse dimension in diastole at rest. Echocardiography was performed within 2 days of radionuclide studies.

Normal controls: Thirty normal subjects were also studied. They ranged in age from 19 to 63 years and had no clinical, electrocardiographic or echocardiographic evidence of cardiovascular or other systemic disease. Each normal subject had normal left ventricular systolic function at rest as indicated by an ejection fraction of 65 percent or greater on echocardiography.[6]

Gated Cardiac Scintigraphy

This procedure was performed with subjects in the supine position at rest and during exercise, as previously described.[3,4] In this procedure, human serum albumin labeled with 10 mCi of technetium-99m is administered intravenously. After the tracer has equilibrated in the blood pool, a conventional Anger camera (field of view = 254 mm diameter) equipped with a high sensitivity parallel hole collimater is oriented in the modified left anterior oblique position[7–9] to isolate the left ventricle in the field of view. Imaging is accomplished with use of a computer-based procedure that is gated to the electrocardiogram, as previously described.[7–11] The spatial resolution of this system is 1 cm.

When this procedure is used, data are collected and concurrently organized into a series of images (framing rate up to 100 frames/sec), residing in the core memory of the computer and spanning the average cardiac cycle. While data are being acquired, these images can be displayed in rapid sequence, that is, in endless-loop flicker-free movie format, so that qualitative information regarding spatial and temporal variation of the cardiac chambers is immediately accessible. Visually interpretable information is produced within 30 seconds of the onset of data collection, and statistically reliable results within 1 to 2 minutes.[10,11] The rapidity of data collection permits the procedure to be applied to studies during exercise, even in patients with exercise-induced symptoms that might preclude prolonged exercise and imaging.[3,4,12,13]

While the cardiac images are being created, the computer simultaneously analyzes the acquired data to produce a time-activity curve with high (10 msec) resolution.[7–11] Corrections for background activity are made as previously described.[7–9] Because blood radioactivity is proportional to blood volume, after correction for background the time-activity curve in fact represents a measure of left ventricular volume versus time. Therefore, once the physician has identified the left ventricle in the end-diastolic movie frame, quantitation of relative left ventricular volume changes with time can be performed.

Statistically reliable information is obtained by summing the radioactivity in the ventricle during many beats. In most studies at least 200 beats, involving more than 2,000,000 total counts, are summed. After each cardiac cycle the length of the R-R interval is automatically examined to determine whether it lies within a physician-selected temporal beat-length window. Cycles falling outside this window are rejected to prevent distortion of the time-activity curve and movie by premature beats. No provision is made for special assessment of patients with intraventricular conduction defects, but no patient in this study had either right or left bundle branch block.

Imaging during exercise: After images and time-activity curves were obtained at rest, the subjects, still in the supine position, began to pedal a bicycle ergometer. Exercise loads were increased in stepwise fashion at 2 minute intervals, with exercise continued until limited by fatigue or, in symptomatic patients, by the development of limiting dyspnea or, rarely, angina pectoris. Imaging was begun when the heart rate reached 10 beats/min below the age-predicted or previously determined maximal heart rate, or at the first indication of the development of symptoms, if this occurred earlier. Imaging continued for at least 2 minutes. Because symptoms occasionally caused patients to stop exercise at heart rates below those achieved by normal subjects at peak exercise, imaging and analysis were undertaken in normal subjects at several intervals during exercise at submaximal as well as maximal heart rates. In all subjects, heart rate and blood pressure (measured using arm cuff sphygmomanometry) were recorded at 1 to 2 minute intervals during exercise.

Determination of ejection fraction: After completion of imaging, left ventricular ejection fraction at rest and during exercise was determined by computer analysis of left ven-

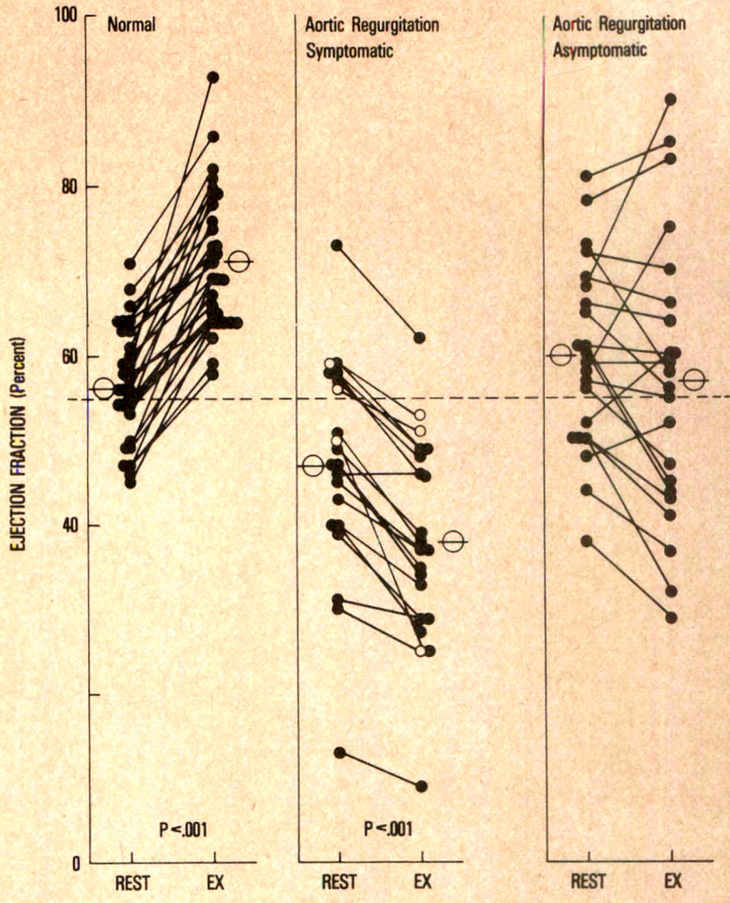

FIGURE 1. Effect of exercise (EX) on left ventricular ejection fraction in symptomatic and asymptomatic patients with aortic regurgitation. **Open circles** represent values from patients with minimal symptoms (see text); **open circles with bars** indicate average ejection fraction values; the **dashed line** at ejection fraction value of 55 percent represents the lower limit of normal during exercise (see text). P = probability.

tricular time-activity curves, as previously described.[7–9] Radionuclide scintigraphic assessment of ejection fraction produces results that correlate very closely with those obtained with contrast angiography ($r = 0.92$, $P < 0.001$)[14]; the variation of ejection fraction at rest in a single patient over 2 hours is 5 percent or less.

In establishing whether the ejection fraction response of patients with aortic regurgitation was normal during exercise, we included as normal ejection fractions that were within the range observed during exercise in our normal volunteers. Thus, an ejection fraction during exercise was considered normal whether it had increased or decreased in comparison with the value at rest so long as the absolute value was within the previously determined normal range.

Left ventricular volumes: At equilibrium, after background correction, the number of radioactive emissions from the left ventricle is proportional to the amount of blood in the left ventricle. Thus, we estimated the magnitude of the change in end-diastolic volume from rest to exercise by comparing the total number of radioactive emissions per millisecond in the left ventricle in the end-diastolic frame of each time-activity curve. The number of emissions collected during exercise was corrected for loss of radioactivity by physical decay and biologic excretion during the 10 to 25 minutes that elapsed between the beginning of the rest and the beginning of the exercise studies. In this time period, decay varied from 3 ± 1 percent (at 10 minutes) to 8 ± 2 percent (at 25 minutes).[15] This method is not sufficiently well developed to allow estimation of absolute left ventricular volumes. However, studies with technetium-filled Lucite® spheres indicate that the method can be used to define relative volumes.[16]

Statistical comparisons were obtained with use of Student's t test, the Fisher Exact Test and analysis of variance.

Results

Normal subjects: In normal subjects the ejection fraction at rest ranged from 45 to 71 percent (average 57 ± 1 percent [standard error]). In this study we used these values to define the range of the normal ejection fraction at rest. In addition, in these normal subjects the ejection fraction invariably increased from rest to exercise (Fig. 1), irrespective of the intensity of load. Thus, the average ejection fraction was 65 ± 1 percent during mild exercise (heart rate 90 to 105 beats/min), 69 ± 1 percent during moderate exercise (heart rate 106 to 120 beats/min) and 71 ± 2 percent (range 58 to 93 percent) during maximal exercise. Compared with the values at rest, the increase in ejection fraction at each heart rate level was statistically significant ($P < 0.001$). The lowest ejection fraction achieved by any subject during any of the three levels of exercise was 55 percent. Therefore, we considered normal ejection fraction during exercise to include all values greater than 55 percent.

Symptomatic patients with aortic regurgitation: Among the 21 symptomatic patients, ejection fraction at rest averaged 47 ± 2 percent (compared with 57 ± 1 percent in normal subjects) (P <0.001) and was within the normal range in 14. However, during maximal exercise it averaged 38 ± 2 percent (compared with 71 ± 2 percent in normal subjects, P <0.001), and was normal in only one patient. Moreover, in all but one symptomatic patient, ejection fraction decreased from rest to exercise (P <0.001 compared with the direction of change in normal subjects). In the one exception, ejection fraction did not change with exercise. Heart rate at maximal exercise averaged 127 beats/min for the group, with a range of 99 to 159, overlapping all three heart rate ranges at which ejection fraction was measured in normal subjects.

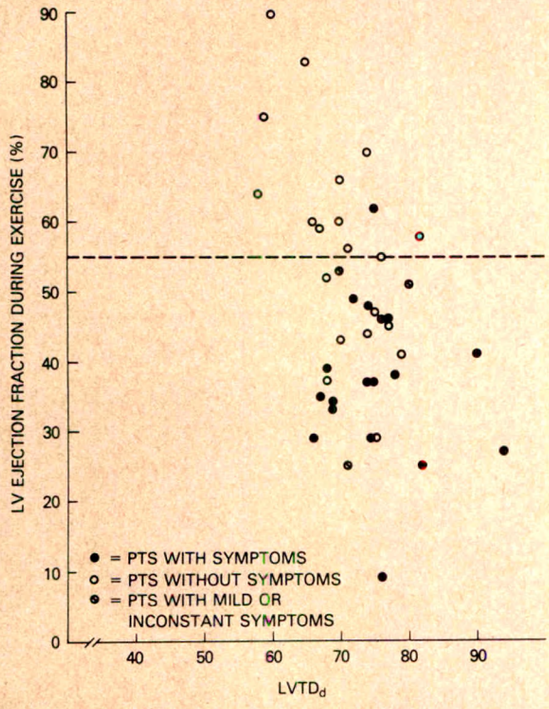

FIGURE 2. Relation between left ventricular (LV) ejection fraction during exercise and echocardiographic left ventricular transverse dimension (LVTD$_d$ expressed in millimeters) at rest. PTS = patients.

Asymptomatic patients with aortic regurgitation: In the 22 asymptomatic patients, the average ejection fraction at rest was 62 ± 2 percent (difference not significant from the value in normal subjects). The ejection fraction was below the normal range at rest (Fig. 1) in only one of these patients, but during maximal exercise, it was below, and occasionally far below, the normal exercise range in nine. Although the ejection fraction increased with exercise in 6 asymptomatic patients, it decreased in 16. During exercise, ejection fraction for the group was 57 ± 3 percent (P <0.001 compared with normal subjects and symptomatic patients). The average heart rate at maximal exercise in asymptomatic patients was 134 beats/min (range 102 to 171), not significantly different from that in symptomatic patients. Moreover, there was no correlation (r = 0) between ejection fraction developed during exercise and maximal heart rate during exercise for either asymptomatic or symptomatic patients.

Relation between ejection fraction and left ventricular size: To determine whether the response to exercise in patients with aortic regurgitation was influenced by left ventricular dilatation, we examined the relation between ejection fraction during exercise and left ventricular size at rest and during exercise. The

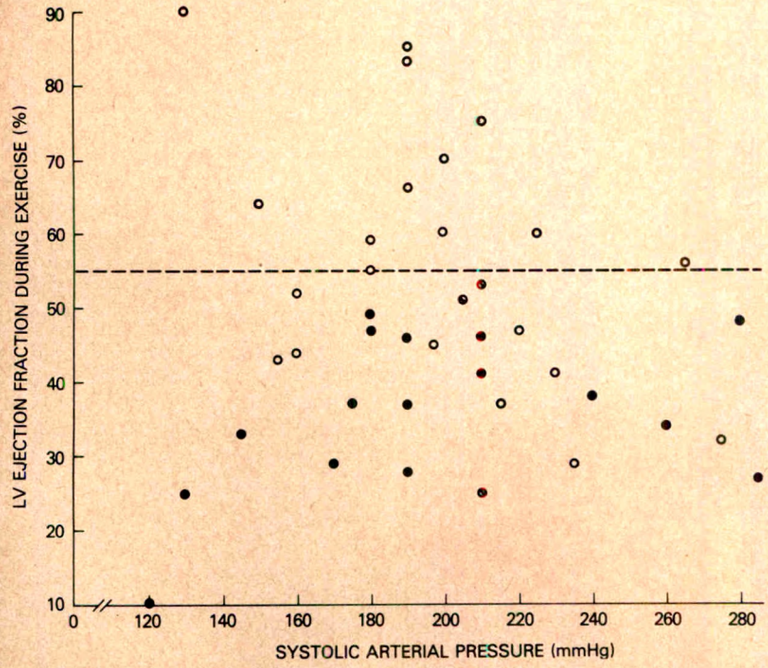

FIGURE 3. Relation between left ventricular (LV) ejection fraction during exercise and peak systolic arterial pressure during exercise. Symbols as in Figure 2.

degree of left ventricular dilatation at rest was assessed by determining the left ventricular transverse dimension in diastole measured with echocardiography. First, a correlation (r = 0.47, P <0.01) was noted between ejection fraction during exercise and diastolic transverse dimension. However, as shown in Figure 2, there was a wide variation in ejection fraction during exercise at any level of diastolic transverse dimension, so that transverse dimension could not be used to predict exercise ejection fraction, either in the whole group or in the subgroup with subnormal ejection fraction during exercise.

Scintigraphic estimation of relative left ventricular end-diastolic volume indicated that this value changed very little during supine exercise in patients with aortic regurgitation (6 percent decrease, P <0.001), and the change did not correlate with the ejection fraction during exercise. End-diastolic volume decreased 6 percent (P <0.01) in the 14 patients with a normal ejection fraction during exercise and 6 percent (P <0.01) in the 29 patients with a subnormal ejection fraction during exercise. In normal subjects end-diastolic volume decreased slightly (3 percent) but not significantly during exercise compared with the values at rest.

Correlation with systolic arterial pressure: There was no correlation between ejection fraction during maximal exercise and peak systolic arterial pressure during exercise (Fig. 3). This was true not only for the entire group but also for patients in the symptomatic and asymptomatic subgroups. Moreover, this lack of correlation was manifest even when patients were grouped according to the degree of left ventricular dilatation as assessed with echocardiography. Finally, peak systolic pressure attained during exercise by normal subjects (range 150 to 245 mm Hg, average 190) demonstrated considerable overlap with the pressure attained by patients with aortic regurgitation (range 120 to 300 mm Hg, average 200), and the difference between the averages was not significant.

Ejection fraction and left ventricular dysfunction: Subnormal ejection fraction during exercise generally appeared before the manifestations of left ventricular dysfunction commonly assessed noninvasively or at cardiac catheterization. Thus, not only was subnormal ejection fraction noted during exercise in 9 of 21 patients (43 percent) with no symptoms and in 20 of 34 patients (59 percent) with a normal ejection fraction at rest, but also in 6 of 10 patients (60 percent) with a normal (less than 15 mm Hg) left ventricular end-diastolic pressure at rest (Fig. 4) and in 6 of 17 patients (35 percent) lacking Romhilt-Estes criteria (5 points or more) for definite left ventricular hypertrophy on electrocardiography (Fig. 5). None of the 13 patients with a left ventricular end-diastolic pressure of 20 mm Hg or greater and only 2 of 17 patients (12 percent) with a Romhilt-Estes score of 6 or more (two abnormalities previously associated with a particularly poor long-term prognosis after operation[17]) had a normal ejection fraction during exercise. There was a correlation, although weak (r = 0.48, P <0.01), between exercise ejection fraction and left ventricular end-diastolic

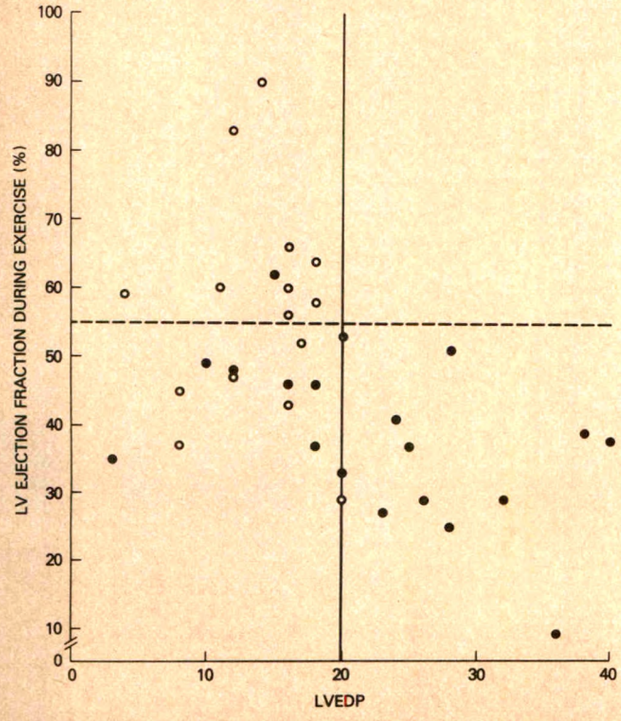

FIGURE 4. Relation between left ventricular (LV) ejection fraction during exercise and left ventricular end-diastolic pressure (LVEDP expressed in mm Hg) at rest. Symbols as in Figure 2. The **solid line** at a left ventricular end-diastolic pressure of 20 represents the previously reported level at or above which long-term postoperative prognosis has been found to be poor (see text).

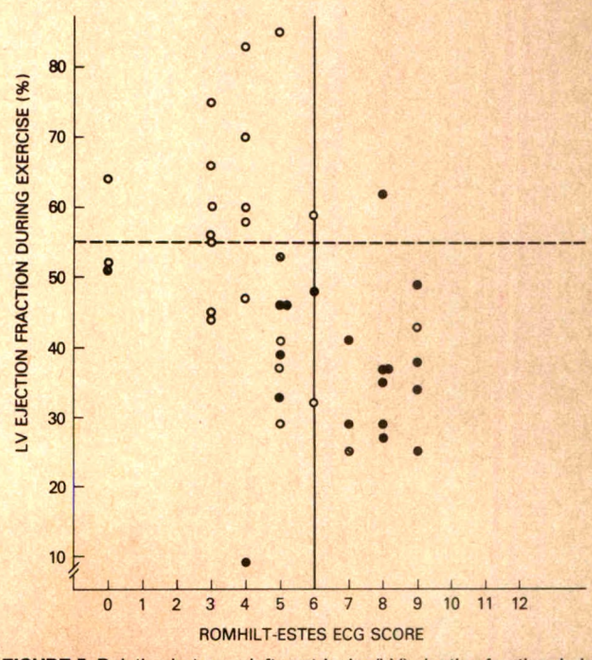

FIGURE 5. Relation between left ventricular (LV) ejection fraction during exercise and Romhilt-Estes electrocardiographic (ECG) score for left ventricular hypertrophy. Symbols as in Figure 2. The **solid line** at a Romhilt-Estes score of 6 represents the level at or above which long-term postoperative prognosis has been found to be poor (see text).

pressure at rest, and between exercise ejection fraction and Romhilt-Estes score ($r = 0.51$, $P < 0.01$).

Discussion

Exercise ejection fraction and left ventricular dysfunction in aortic regurgitation: Our results indicate that in many patients with severe aortic regurgitation ejection fraction is subnormal during exercise, even if it is normal at rest. Thus, although the ejection fraction was subnormal at rest in only 8 of our 43 patients (19 percent) with aortic regurgitation, it was abnormal during exercise in 29 (67 percent). Moreover, even patients who are totally asymptomatic and who have a normal ejection fraction at rest may manifest a subnormal ejection fraction during exercise.

The development of impaired left ventricular function during exercise is not surprising. It has been demonstrated that patients with severe aortic regurgitation as well as other forms of heart disease[1,3,4,18–21] may exhibit normal cardiac function at rest, dysfunction becoming apparent only when the available functional reserve is exceeded. Previous demonstrations of these stress-induced abnormalities have often involved the use of invasive techniques, which are impractical for routine or repeated evaluation. Radionuclide cineangiography affords a relatively safe, simple and noninvasive method allowing repeated evaluation during physiologic stress over prolonged periods of follow-up.

In these patients with severe aortic regurgitation an abnormal ejection fraction during exercise could not be predicted from symptoms, a normal ejection fraction measured at rest, the degree of left ventricular dilatation, the peak systolic pressure attained during exercise or a combination of these factors. In addition, the exercise ejection fraction was often subnormal when left ventricular end-diastolic pressure was normal at rest or when electrocardiographic criteria for left ventricular hypertrophy were lacking.

The response of ejection fraction during exercise seems, therefore, to represent a sensitive and potentially useful clinical index of the functional status of the left ventricle in patients with aortic regurgitation. This conclusion is consistent with the results of earlier studies on the effect of stress on left ventricular function in such patients. Thus, Bolen et al.,[2] utilizing angiotensin to increase afterload in 14 patients with isolated aortic regurgitation (many with normal left ventricular function at rest), demonstrated that despite similar increments in aortic pressure and end-diastolic volume during angiotensin administration, cardiac index and ejection fraction did not change in half the patients and decreased significantly in the other half. Considerable overlap in pre-angiotensin values for end-diastolic volume, ejection fraction and aortic pressure, and in post-angiotensin regurgitant fraction, existed between the two groups.

Exercise ejection fraction and contractile state of myocardium: Abnormality in the ejection fraction during exercise does not necessarily indicate impairment in the intrinsic contractile state of the myocardium, because ejection fraction is also affected by alteration in preload and afterload. Thus, Urschel et al.[22] demonstrated that acute volume loading increases ejection fraction, and Ross and McCollogh[23] found similar results in assessing the effects of chronic volume loading in aortic regurgitation. In addition, the development of an acute pressure load during exercise might preclude an increase in ejection fraction even if ventricular function were normal.[24] However, the presence of important intrinsic left ventricular dysfunction in patients with aortic regurgitation and an abnormal ejection fraction response to exercise is suggested by preliminary studies indicating that ejection fraction during exercise, although improved, most often does not revert to normal even after preload and afterload are reduced or after aortic valve replacement.[12]

In any case, the potential utility of radionuclide cineangiography during exercise may not depend on whether an abnormal ejection fraction always indicates intrinsic myocardial dysfunction. Just as ejection fraction at rest is a valuable guide to the functional status of the left ventricle[25] and to prognosis,[26,27] ejection fraction during exercise might be expected to prove valuable empirically as an early indicator of diminished left ventricular functional reserve and, perhaps, of prognosis. This is a particularly intriguing possibility, because abnormalities in exercise ejection fraction occur relatively early in patients with severe aortic regurgitation, before the development of symptoms or of abnormal ejection fraction at rest, and occasionally before abnormalities in left ventricular end-diastolic pressure or electrocardiographic evidence of left ventricular hypertrophy.

Clinical implications: When the natural history of patients with aortic regurgitation is considered, the presence of left ventricular dysfunction induced only by stress probably represents an intermediate point between normal left ventricular function and the development of left ventricular dysfunction at rest. The present study indicates that radionuclide cineangiography is uniquely suited for periodic assessments aimed at detecting early development of left ventricular dysfunction. If follow-up studies demonstrate a relation between exercise ejection fraction and natural history, evaluation with radionuclide cineangiography may provide critically important information that could lead to a reassessment of the appropriate timing of operative intervention.

Acknowledgment

We gratefully acknowledge the technical assistance of Susan Farkas and the aid of William Smith in assembling these data. We are also grateful for the assistance during cardiac catheterization studies given by Fred Bullock, John Condit, Nancy Condit, Carolyn Ewels, Mary Denise Ochsenshlager and Marjory Rimmer.

References

1. **Lewis RP, Bristow JD, Griswold HE:** Exercise hemodynamics in aortic regurgitation. Am Heart J 80:171–176, 1970
2. **Bolen JL, Holloway EL, Zener JC, et al:** Evaluation of left ventricular function in patients with aortic regurgitation using afterload stress. Circulation 53:132–138, 1976
3. **Borer JS, Bacharach SL, Green MV, et al:** Real-time radionuclide cineangiography in the noninvasive evaluation of global and regional left ventricular function at rest and during exercise in patients with coronary artery disease. N Engl J Med 296:839–844, 1977
4. **Borer JS, Bacharach SL, Green MV, et al:** Effects of nitroglycerin on exercise-induced abnormalities of left ventricular regional function and ejection fraction in coronary artery disease: assessment by radionuclide cineangiography in symptomatic and asymptomatic patients. Circulation 57:314–320, 1978
5. Criteria Committee of the New York Heart Association: Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels, seventh edition. Boston, Little, Brown, 1973, p 286
6. **Gardin JM, Henry WL, Savage DD, et al:** Echocardiographic evaluation of an older population without clinically apparent heart disease (abstr). Am J Cardiol 39:277, 1977
7. **Green MV, Ostrow HG, Douglas MA, et al:** High temporal resolution ECG-gated scintigraphic angiocardiography. J Nucl Med 16:95–98, 1975
8. **Green MV, Bacharach SL, Douglas MA, et al:** The measurement of left ventricular function and the detection of wall motion abnormalities with high temporal resolution ECG-gated scintigraphic angiocardiography. IEEE Trans Nucl Sci NS 23:1257–1263, 1976
9. **Douglas MA, Ostrow HG, Green MV, et al:** A computer processing system for ECG-gated radioisotope angiography of the human heart. Comput Biomed Res 9:133–142, 1976
10. **Bacharach SL, Green MV, Borer JS, et al:** A real-time system for multi-image gated cardiac studies. J Nucl Med 18:79–84, 1977
11. **Bacharach SL, Green MV, Borer JS, et al:** Real-time scintigraphic cineangiography. St. Louis, Missouri, Computers in Cardiology, Proceedings of IEEE Computer Society, 1976, p 45–48
12. **Borer JS, Bacharach SL, Green MV, et al:** Left ventricular function during exercise before and after aortic valve replacement (abstract). Circulation 56:Suppl III:III-28, 1977
13. **Borer JS, Kent KM, Bacharach SL, et al:** Accuracy of radionuclide cineangiography in detecting coronary artery disease: comparison with exercise electrocardiography (abstr). Circulation 56:Suppl III:III-33, 1977
14. **Green MV, Douglas MA, Brody W, et al:** A count based method for determination of ejection fraction from radionuclide angiograms. J Nucl Med, in press
15. **Borer JS, Bacharach SL, Green MV, et al:** Evaluation of the clinical utility of real-time computer-based radionuclide cineangiography. Rotterdam, The Netherlands, Computers in Cardiology, Proceedings of IEEE Computer Society, 1977, p 3–8
16. **Bacharach SL, Green MV, Borer JS, et al:** ECG-gated scintillation probe measurement of left ventricular function. J Nucl Med 18: 1176–1183, 1977
17. **Hirshfeld JW, Epstein SE, Roberts AJ, et al:** Indices predicting long-term survival after valve replacement in patients with aortic regurgitation and patients with aortic stenosis. Circulation 50: 1190–1199, 1974
18. **Bishop JM, Wade OL:** Relationships between cardiac output and rhythm, pulmonary vascular pressures and disability in mitral stenosis. Clin Sci 24:391–404, 1963
19. **Epstein SE, Beiser GD, Stampfer M, et al:** Characterization of the circulatory response to maximal upright exercise in normal subjects and patients with heart disease. Circulation 35:1049–1062, 1967
20. **Ross J:** The assessment of myocardial performance in man by hemodynamic and cineangiographic techniques. Am J Cardiol 23:511–515, 1969
21. **Ross J, Braunwald E:** The study of left ventricular function in man by increasing resistance to ventricular ejection with angiotension. Circulation 29:739–749, 1964
22. **Urschel CW, Covell JW, Graham TP, et al:** Effects of acute valvular regurgitation on the oxygen consumption of the canine heart. Circ Res 23:33–43, 1968
23. **Ross J, McCollogh WH:** Nature of enhanced performance of the dilated left ventricle in the dog during chronic volume overloading. Circ Res 30:549–556, 1972
24. **Taylor RR, Cingolani HE, McDonald RH:** Relationship between left ventricular volume, ejected fraction, and wall stress. Am J Physiol 211:674–680, 1966
25. **Dodge HT, Baxley WA:** Left ventricular volume and mass and their significance in heart disease. Am J Cardiol 23:528–537, 1969
26. **Rigo P, Murray M, Strauss HW, et al:** Left ventricular function in acute myocardial infarction evaluated by gated scintiphotography. Circulation 50:678–684, 1974
27. **Clark CE, Henry WL, Morganroth J, et al:** Influence of ejection fraction on the results of operation in aortic regurgitation (abstr). Circulation 52:Suppl II:II-169, 1975

Prevalence of Right Ventricular Involvement in Inferior Wall Infarction Assessed With Myocardial Imaging With Thallium-201 and Technetium-99m Pyrophosphate

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To assess the prevalence and clinical relevance of right ventricular involvement in acute inferior wall infarction, 78 consecutive patients with the latter condition were studied with thallium-201 and technetium-99m pyrophosphate myocardial imaging. Right ventricular involvement was determined from superimposition of the 45° left anterior oblique thallium-201 and technetium-99m pyrophosphate images. All 78 patients showed thallium-201 defects. Sixty-four patients had positive pyrophosphate scans, and 24 of these (37.5 percent) showed right ventricular involvement. None of the patients with right ventricular involvement in this consecutive series showed the classic signs of severe right ventricular failure, although subclinical right ventricular dysfunction may have been present. There was no significant difference in the incidence of cardiogenic shock between the groups with and without right ventricular involvement. It is concluded that right ventricular involvement in acute inferior wall infarction is relatively frequent but not necessarily associated with severe right-sided pump failure. In patients with acute inferior wall infarction and severe pump failure, dual imaging provides a simple noninvasive method of identifying the subgroup of patients with right ventricular involvement who may benefit from volume loading.

The recognition of right ventricular involvement in acute inferior wall infarction has attracted increasing interest.[1,2] The initial description[1] of this pathophysiologic event included data on six patients with hypotension and frank shock manifesting disproportionately elevated right ventricular filling pressures and a favorable therapeutic response to volume expansion. Although right ventricular infarction without shock was initially considered a relatively rare phenomenon,[3] more recent pathologic and clinical studies[4–8] suggest that it may be relatively common in inferior infarction. The true prevalence and the clinical relevance of right ventricular involvement in infarction has not been established. This study was undertaken to evaluate the prevalence and clinical implications of right ventricular involvement in acute inferior wall infarction as determined noninvasively with dual thallium-201 and technetium-99m pyrophosphate myocardial imaging.

Material and Methods

Patient population: Seventy-eight consecutive patients with electrocardiographic evidence of acute inferior wall infarction were studied with thallium-201 and technetium-99m pyrophosphate scintigraphy. There were 58 men and 20 women whose ages ranged from 43 to 80 years (average 55 years). All patients had an acute myocardial infarction with a history of sustained chest pain, the development of Q waves of 0.04 second's duration and characteristic evolutionary changes in serum enzymes (glutamic oxaloacetic transaminase, lactic dehydrogenase, MB creatine kinase). The electrocardiographic site of infarction was determined according to the criteria of the New York Heart Association.[9] No patient had sustained a previous infarction.

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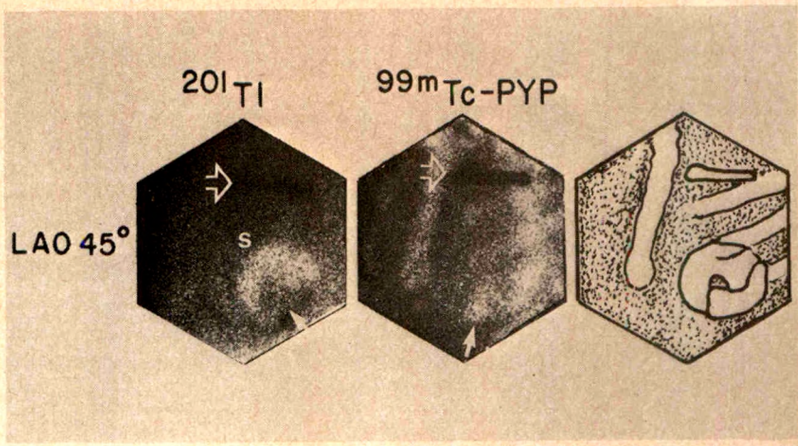

FIGURE 1. Method of determining right ventricular involvement with dual myocardial imaging. During both studies a lead marker is taped to the chest wall within the field of view (**open arrow**). This spatial reference allows accurate superimposition of schematic drawings of the images. The thallium-201 (^{201}Tl) image (**left**) shows an inferoposterior defect (**solid arrow**). In the left anterior oblique (LAO) 45° view, the site of the interventricular septum (s) separates the area of the right and left ventricles. The technetium-99m pyrophosphate image (^{99m}Tc-PYP) (**center**) shows 3+ accumulation at the inferior wall (**solid arrow**). Superimposition of schematic drawings of both images (**right**) shows that the abnormal technetium-99m pyrophosphate accumulation is located lateral to the interventricular septum and is therefore in the left ventricle. Because no uptake is seen anterior to the interventricular septum, right ventricular involvement is not present.

Scintigraphy: All patients were studied with thallium-201 scintigraphy shortly after their admission within 20 hours (mean 10 hours) after the onset of infarction and subsequently underwent imaging with technetium-99m pyrophosphate. Pyrophosphate scintigraphy was performed at least 24 hours (mean 32 hours) after the onset of symptoms of acute myocardial infarction. Because the left anterior oblique views were made with the patient in the supine position and with 45° angulation of the detector head of the gamma camera, accurate repositioning of the patient, even on two consecutive days, could be done readily. During both scintigraphic studies, lead markers were taped in the same marked place on the chest wall of each patient. These markers were within the field of view and provided a spatial reference that allowed subsequent accurate superimposition of the images.

Myocardial imaging with thallium-201 was started 5 minutes after injection of 1.7 to 2.7 mCi of thallium. Imaging with technetium-99m pyrophosphate was started 1.5 to 2 hours after injection of 12 mCi of this agent. Analog images were obtained with an Ohio Nuclear ON100 scintillation camera, using a low energy high resolution parallel hole collimator. The energy window (20 percent) was symmetrically set over 75 kev for thallium-201 and 140 kev for technetium-99m pyrophosphate. For each study scintiscans were obtained in three different positions (anterior 0°, left anterior oblique 45° and left lateral 90°, the latter with the patient lying on his right side). For each image 300,000 counts were accumulated.

Analysis and comparison of thallium-201 and technetium-99m pyrophosphate images: Unprocessed analog images were analyzed to determine the location and extent of diminished thallium-201 activity and abnormal technetium-99m pyrophosphate accumulation. The thallium-201 scintiscans were graded as positive, questionable or normal according to previously published techniques.[10] The judgment of diminished or absent activity was made qualitatively by comparing thallium-201 accumulation in different areas of the myocardium of the left ventricle. Scintiscans graded positive (indicating a defect) showed a consistent area of definite diminished thallium-201 activity, equal to or less than lung activity, in all three views. Questionable scans were those with either a consistent area with diminished activity but slightly higher than background activity in all three views or a defect in only one view. Normal scans showed homogeneous thallium uptake in the left ventricle in all three views. The accurate extent of an area of diminished activity—that is, involvement of lateral wall or septum—was noted. Statistical analysis was performed using the Fisher Exact test. The intensity of technetium-99m pyrophosphate uptake was graded 0 to 4+ according to the scheme devised by Parkey et al.[11] Zero represented no activity, 1+ questionable activity, 2+ definite activity in the myocardium equal in intensity to that in the ribs, 3+ activity equal to that in the sternum and 4+ activity exceeding sternal activity. Scintiscans showing pyrophosphate activity of 2+ or more in the left ventricle were considered positive. In addition, the pattern of activity was judged to be focal or diffuse. The interpretation of scintiscans in this study represented a consensus of independent evaluations by two observers.

Right ventricular involvement was determined as follows: In the 45° left anterior oblique images the interventricular septum, as visualized with thallium-201, separates the area of the right and left ventricles. A schematic drawing of the thallium-201 image of the left ventricle and the position of the lead markers in the left anterior oblique view was made on transparent paper. This drawing (Fig. 1) was then superimposed on the left anterior oblique view of the technetium-99m pyrophosphate image. Technetium-99m pyrophosphate activity located lateral to the interventricular septum was interpreted as left ventricular activity, whereas activity located anterior to the septum and adjacent to the activity of the sternum was interpreted as right ventricular activity.

Estimation of pump failure: The presence of congestive heart failure was judged from the physical examination. Hemodynamic monitoring with a Swan-Ganz catheter was performed only in patients with severe pump failure. Right-sided congestive heart failure was assessed from clinical estimation of venous pressure, evaluation for neck vein distension and the presence of peripheral edema. Left-sided congestive heart failure was determined clinically from the presence of pulmonary rales, a third heart sound gallop, radiographic assessment of pulmonary congestion or cardiomegaly, and urinary output. Killip's classification[12] was used to categorize these patients: class I, no signs of pump failure; class II, rales over 50 percent or less of the lung fields; class III, pulmonary edema; and class IV, cardiogenic shock.

Results

Thallium-201 and technetium-99m pyrophosphate scintigraphy (Table I): All 78 patients showed a defect at the inferior or inferoposterior wall in the thallium-201 scintiscans. The technetium-99m pyro-

TABLE I
Results in 78 Consecutive Patients With Acute Inferior Infarction

Thallium-201 Positive	Technetium-99m Pyrophosphate Positive (≥++)	Technetium-99m Pyrophosphate Negative
78/78	64/78	14/78
	LV+RV− 40/64	LV+RV+ 24/64 (37.5%)

LV+RV+ = abnormal accumulation of technetium-99m pyrophosphate in both the left and right ventricles. LV+RV− = abnormal technetium-99m pyrophosphate accumulation in the left but not the right ventricle.

phosphate scintiscans showed abnormal (2+ or more) focal left ventricular activity at the inferior wall in 64 of 78 patients (82 percent). Superimposition of the left anterior oblique views with the lead markers as reference points showed uptake of technetium-99m pyrophosphate in the right ventricle in 24 of 64 patients (37.5 percent) (Group A). Examples from these patients are shown in Figure 2. Thirteen patients in Group A showed technetium-99m pyrophosphate activity equal to that in the left ventricle, whereas in 11 patients right ventricular technetium-99m pyrophosphate activity was slightly less than in the left ventricle. In 40 patients with positive pyrophosphate scans *no* accumulation was present in the area of the right ventricle (Group B). Fourteen of the 78 patients had negative pyrophosphate scans (Group C). In 7 of these 14 patients the intensity of accumulation was 1+ and diffuse; in 7 other patients no activity was present. In these 14 patients imaging was performed at a mean time interval of 28 hours after the onset of infarction. Technetium-99m pyrophosphate imaging was not repeated in these patients.

In 25 of 78 patients the defect in the thallium-201 scans also partly involved the interventricular septum. The prevalence of septal involvement was greater in Group A (12 of 23 patients) than in Group B (10 of 40 patients). This difference is significant ($P = 0.03$) when verified with the Fisher Exact test.

Incidence of congestive heart failure (Table II): Left-sided congestive heart failure occurred in 18 of 78 patients. The incidence of congestive heart failure was not significantly different among Groups A, B and C. Cardiogenic shock occurred in two patients in Group A, three patients in Group B and two patients in Group C.

Only one patient in this study showed signs of moderate right-sided congestive heart failure. This patient had 2+ technetium-99m pyrophosphate uptake in the right ventricle. The clinical course in this patient was normal after conventional treatment with diuretic drugs and digitalis.

Causes of death: Eight of the 78 patients died. Two of these patients had negative technetium-99m pyrophosphate scintiscans; both patients died from cardiogenic shock. Three of 24 patients in Group A died, 2 from cardiogenic shock and 1 from cardiac rupture. In Group B, 3 of 40 patients died from cardiogenic shock.

Discussion

In this study thallium-201 scintigraphy appeared to be considerably more sensitive than technetium-99m pyrophosphate in detecting acute myocardial infarction. This can be explained by the relatively early performance of the thallium-201 studies—within 20 hours after infarction, a period when the sensitivity level of the method is high.[10] On the other hand, technetium-99m pyrophosphate imaging was not repeated in patients who had a negative scan. Although these studies were performed at an appropriate time interval of at least 24 hours after infarction, it is possible that some studies that later became positive were not included.

Prevalence of right ventricular involvement in acute inferior wall infarction: Our data indicate that right ventricular involvement occurs in 37.5 percent of patients with acute inferior wall infarction. We assumed

TABLE II
Relation Between Results of Technetium-99m Pyrophosphate Imaging and Incidence of Congestive Heart Failure and Cause of Death

Group	PYP_{LV}	PYP_{RV}	LCHF Class I	LCHF Class II	LCHF Class III	LCHF Class IV	RCHF	Cause of Death CR	Cause of Death CS
Group A (24 pts)	≥++	≥++	18	3		2	1	1	2
Group B (40 pts)	≥++	−	30	6	1	3			3
Group C (14 pts)	+	−	6	1					
	−	−	5			2			2

CR = cardiac rupture; CS = cardiogenic shock; LCHF class = Killip's classification[12] for left-sided congestive heart failure; PYP_{LV} = technetium-99m pyrophosphate uptake in the left ventricle; PYP_{RV} = technetium-99m pyrophosphate uptake in the right ventricle; RCHF = right-sided congestive heart failure.
++, + and − = grading for technetium-99m pyrophosphate uptake (see text).

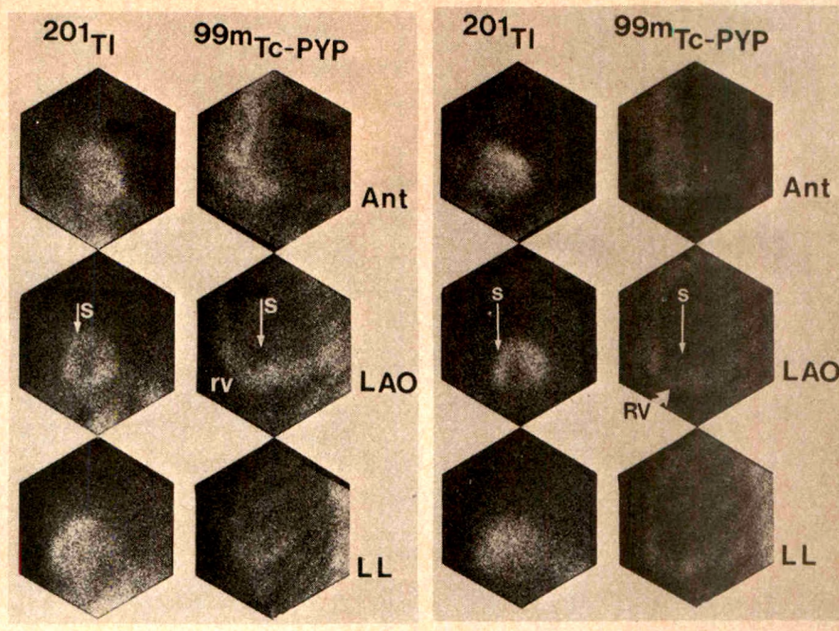

FIGURE 2. Dual imaging with thallium-201 (^{201}Tl) and technetium-99m pyrophosphate (^{99m}Tc-PYP) in patients with acute inferior wall infarction and right ventricular involvement without clinical signs of severe right ventricular failure. **Left,** thallium-201 scintiscans show an inferoposterior defect well visualized in the anterior (Ant) and left lateral (LL) views. The left anterior oblique (LAO) view in the technetium-99m pyrophosphate image shows the typical horizontal platelike activity of an inferior wall infarction. The spatial reference provided by the lead marker reveals that this activity also involves the right ventricle (rv). **Right,** thallium-201 scintiscans show an inferoposterior defect in all three views. The technetium-99m pyrophosphate left anterior oblique image shows characteristic ω-shaped activity due to uptake in the interventricular septum (s) (**arrow**) and in the right ventricle.

in our study that technetium-99m pyrophosphate accumulation in the right ventricle indicates myocardial damage. This assumption seems appropriate because Sharpe et al.[7] recently reported that technetium-99m pyrophosphate uptake in the right ventricle correlated with right ventricular dysfunction as judged from gated blood pool imaging.

The reported prevalence of right ventricular infarction varies greatly. In 1934 Appelbaum et al.[3] reported a prevalence rate of 7 percent in a postmortem study. In 1970 Harnarayan et al.[13] reported right ventricular involvement in 85 percent of the patients who died from cardiogenic shock after acute myocardial infarction. These differences can be explained by differences in patient population, myocardial staining techniques and the introduction of coronary care units, which made prolonged survival of patients with severe myocardial damage possible. Since the description by Cohn et al.[1] of the clinical findings in patients with right ventricular infarction, three studies in relatively small series of patients suggested a relatively high frequency of right ventricular involvement in inferior wall infarction. Rigo et al.[6] and Sharpe et al.[7] used gated blood pool images to visualize right ventricular dysfunction. Their studies indicated a prevalence rate of 43 and 40 percent, respectively. Recently Reduto et al.[8] reported abnormal right ventricular ejection fraction as assessed from a radionuclide first-pass method in 50 percent of the patients with acute inferior wall infarction.

Clinical relevance: The initial report on right ventricular infarction[1] emphasized that severe pump failure may develop and the patients may present the clinical findings of cardiogenic shock. Recognition of this condition was considered important because volume loading resulted in a striking improvement of cardiac output and clinical survival.[6] In the present study, right

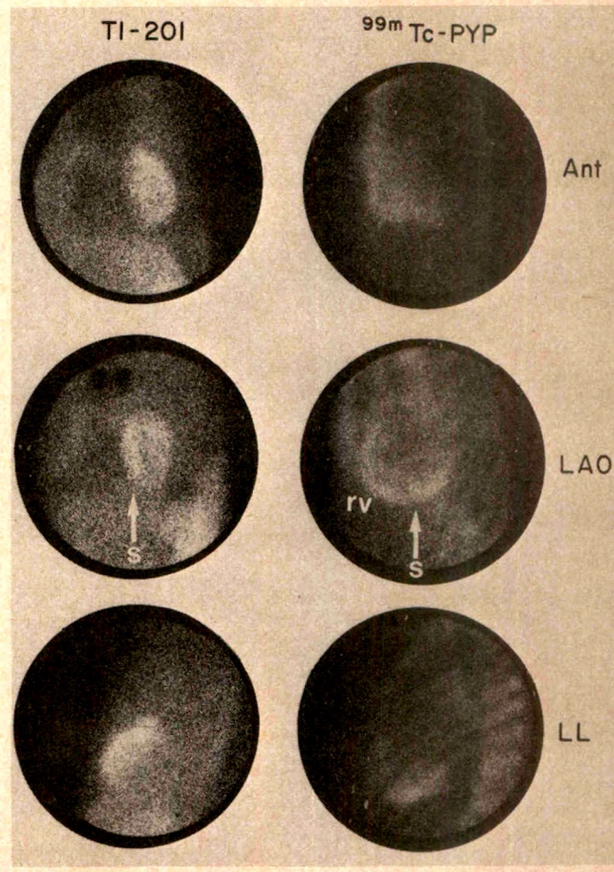

FIGURE 3. Dual imaging with thallium-201 and technetium-99m pyrophosphate in a patient with an acute inferior wall infarction and right ventricular involvement and the classic clinical symptoms of severe right ventricular failure. Note that the amount of technetium-99m pyrophosphate accumulation in the right ventricle is more impressive than that in the images in Figure 2. Abbreviations as in Figure 2.

ventricular involvement, as assessed from technetium-99m pyrophosphate accumulation, was relatively frequent; however, no patient had severe right ventricular failure. Only one patient with positive technetium-99m pyrophosphate uptake in the right ventricle showed moderate evidence of elevated central venous pressure and systemic venous engorgement. Although it is possible that right ventricular infarction was not recognized in the patients with cardiogenic shock, these patients showed right ventricular filling pressures within normal limits and significantly evaluated pulmonary wedge pressures consistent with severe left ventricular failure. The incidence of cardiogenic shock was not different in the group with and without right ventricular involvement. In light of the data of Sharpe et al.[7] it seems very likely that subclinical right ventricular dysfunction is present in patients with technetium-99m pyrophosphate uptake in the right ventricle. In the study by Reduto et al.[8] the right ventricular ejection fraction was decreased without clinical signs of right ventricular failure.

After completion of this study in a consecutive series of patients, we studied two separate patients, who presented with the classic clinical findings of right ventricular involvement reported by Cohn et al.[1]: low cardiac output and elevated right ventricular pressures, responding with an increase of cardiac output on volume loading. These patients (Fig. 3) showed more impressive technetium-99m pyrophosphate uptake in the right ventricle than the patients with subclinical right ventricular involvement in the consecutive series. This finding suggests that the extent of right ventricular damage determines the presence or absence of typical clinical symptoms.

Clinical implications: Our study suggests that right ventricular involvement in acute inferior wall infarction is relatively frequent but is not necessarily associated with severe pump failure. Many of these patients may have subclinical right ventricular dysfunction. In patients with acute inferior wall infarction and signs of severe pump failure, dual imaging with thallium-201 and technetium-99m pyrophosphate provides a simple noninvasive method of recognizing the subgroup of patients who may have hemodynamic deterioration due to major right ventricular involvement. Appreciation of the condition and subsequent appropriate treatment with volume loading might be life-saving in this group.

References

1. **Cohn JN, Guiha NH, Brodler MI, et al:** Right ventricular infarction. Clinical and hemodynamic features. Am J Cardiol 33:209–214, 1974
2. **Rotman M, Ratliff NB, Hawley J:** Right ventricular infarction: a haemodynamic diagnosis. Br Heart J 36:941–944, 1974
3. **Appelbaum E, Nicolson GHB:** Occlusive disease of the coronary arteries. Am Heart J 10:662–680, 1934
4. **Erhardt LR, Sjogren A, Wahlberg I:** Single right-sided precordial lead in the diagnosis of right ventricular involvement in inferior myocardial infarction. Am Heart J 91:571–576, 1976
5. **Erhardt LR:** Right ventricular involvement in acute myocardial infarction. Eur J Cardiol 4:411–418, 1976
6. **Rigo P, Murray M, Taylor DR, et al:** Right ventricular dysfunction detected by gated scintiphotography in patients with acute inferior myocardial infarction. Circulation 52:268–274, 1975
7. **Sharpe DN, Botvinick EH, Shames DM, et al:** The noninvasive diagnosis of right ventricular infarction. Circulation 57:483–490, 1978
8. **Reduto LA, Berger HJ, Cohen LS, et al:** Sequential radionuclide assessment of left and right ventricular performance after acute myocardial infarction. Ann Intern Med, in press
9. The Criteria Committee of The New York Heart Association: Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels, seventh edition. Boston, Little, Brown, 1973
10. **Wackers FJT, Busemann Sokole E, Samson G, et al:** Value and limitations of thallium-201 scintigraphy in the acute phase of myocardial infarction. N Engl J Med 295:1–5, 1976
11. **Parkey RW, Bonte FJ, Meyer SL, et al:** A new method for radionuclide imaging of acute myocardial infarction in humans. Circulation 50:540–546, 1974
12. **Wolk MJ, Scheidt S, Killip T:** Heart failure complicating acute myocardial infarction. Circulation 45:1125–1138, 1972
13. **Harnarayan C, Bennett MA, Pentecost BL, et al:** Quantitative study of infarcted myocardium in cardiogenic shock. Br Heart J 32: 728–732, 1970

Metabolic Responses of the Heart in Acute Myocardial Infarction in Man

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Acute myocardial infarction evokes a characteristic neurohumoral response: Catecholamine release is increased, plasma contents of free fatty acids and glucose are elevated and glucose tolerance is diminished. To what degree the myocardium participates in this stress response was evaluated by sampling coronary sinus and arterial blood in 50 patients with acute transmural infarction. Studies were initiated an average of 8 hours after the clinical onset of infarction and were continued for up to 60 hours. A total of 173 separate metabolic studies were analyzed. Forty-one percent exhibited a pattern of predominant myocardial free fatty acid uptake (mean extraction ratio 24 percent) in the presence of elevated plasma free fatty acid and glucose contents (respective means 1,181 μmol/liter and 210 mg/100 ml). Myocardial extraction ratios for glucose, lactate and pyruvate were low (respective means 1.1, 4 and 11 percent). Twenty-one percent of the studies revealed normal myocardial metabolism and 18 percent showed enhanced carbohydrate uptake, as evidenced by increased myocardial extractions of lactate and pyruvate (respective means 42 percent) and of glucose (mean 5 percent). Plasma contents of glucose and free fatty acids were lower than in the predominant free fatty acid group (respective means 156 mg/100 ml and 743 μmol/liter). The remaining 20 percent of studies showed high plasma substrate contents and low myocardial substrate uptake suggesting metabolic breakdown. The free fatty acid metabolic pattern was observed in more than 50 percent of the studies performed at the time of or close to the occurrence of important clinical complications. Propranolol, 0.1 mg/kg intravenously, shifted myocardial substrate utilization from free fatty acids toward carbohydrates. The myocardial respiratory quotient increased from an average of 0.79 to 0.88 ($P < 0.01$).

The study demonstrates that the metabolic patterns of the myocardium are influenced by the systemic response to stress. Beta adrenergic blockade changed substrate utilization of the myocardium, supporting the hypothesis that adrenergic activation plays an important role in these metabolic responses.

Various studies during the past two decades[1–7] have shown that patients with acute myocardial infarction exhibit changes in carbohydrate metabolism similar to those of diabetes mellitus. Studies[2,6,7–11] have also demonstrated elevation of plasma free fatty acid contents in the early hours after acute myocardial infarction. Exaggerated catecholamine release may account for abnormalities in both carbohydrate and lipid metabolism.

Raab et al.[12] showed more than 20 years ago that stellate ganglion stimulation or catecholamine administration could produce myocardial ischemia in animals with decreased coronary reserve. The observation of Oliver et al.[13,14] that death and cardiac arrhythmias were correlated with elevations of plasma free fatty acids in patients with acute myo-

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cardial infarction suggested that enhanced sympathetic activity with consequent lipolysis, elevation of plasma free fatty acid and glucose contents, and stimulation of myocardial contractility might limit survival after infarction.

The introduction of coronary sinus cannulation in man by Bing et al.[15] allowed measurement of myocardial metabolism in the normal and diseased heart. Bing and his co-workers[16,17] demonstrated that myocardial uptake of glucose and free fatty acids was dependent on plasma concentrations and that free fatty acids were important substrates for the heart under stress. Interactions between glucose and free fatty acid metabolism were described by Randle et al.,[18] who presented evidence that carbohydrate intolerance could be due to high plasma levels of free fatty acids and ketone bodies; insulin deficiency was not necessary. The present study was designed to determine to what degree the myocardium in patients with acute infarction participates in this systemic stress response.

Methods

Selection of patients: Patients were considered for study if the following criteria for acute transmural myocardial infarction were met: development or presence of Q waves, acute elevation of S-T segments, rise in serum creatine kinase level and a history characteristic of acute myocardial infarction. The initial study was performed within 12 hours after the clinical onset of infarction. The protocol for hemodynamic and metabolic evaluation was approved by the Human Experimentation Committee of this institution. Consent was obtained from the patient, who was informed that two catheters would be inserted and left in place for approximately 3 days while hemodynamic and metabolic measurements were obtained. The patient was aware that the results of the study might not necessarily benefit him at present but that they would contribute to the understanding of acute ischemic heart disease.

Experimental procedure: A no. 7 Goodale Lubin catheter was placed into the pulmonary artery; a no. 19 Teflon® catheter was inserted into the brachial artery after puncture of the surgically exposed radial artery. After determination of initial hemodynamic data, the Goodale Lubin catheter was pulled back from the pulmonary artery and guided with fluoroscopic control into the middle portion of the coronary sinus. The position of the catheter tip was checked with injection of Hypaque® (sodium diatrizoate). Vascular pressures were measured with P23d Statham strain gauges and recorded on a multichannel oscilloscopic recorder (Electronics for Medicine).

Each initial study included measurement of cardiac output, pulmonary arterial and capillary wedge pressures, intravascular arterial pressure, heart rate and coronary blood flow and analysis of substrates in the arterial and coronary sinus blood. Measurements of heart rate and arterial pressures and metabolic evaluations were repeated at approximately 12 hour intervals up to 60 hours. All patients received intravenous infusion of 5 percent dextrose in water, approximately 750 to 1,000 ml the first 12 hours. The coronary sinus catheter was kept patent with infusion of normal saline solution using a constant infusion pump. No heparin was used. During the first 12 hours of observation, the patient received no food or liquid by mouth except for sips of water. During the subsequent 48 hours a liquid diet was served consisting of clear broth, Jello® and decaffeinated coffee with milk. Five percent dextrose in water was administered intravenously to maintain the total fluid intake at approximately 1,500 to 2,000 ml per 24 hours.

Methods of analysis: Samples of arterial and coronary sinus blood were obtained simultaneously. Details about sampling techniques, determinations of plasma content of lactate, pyruvate, pH, oxygen and carbon dioxide tensions were previously published.[19] Oxygen and carbon dioxide contents were measured with the van Slyke manometric method.[20] Plasma free fatty acid content was determined with the method of Dole,[21] as modified by Trout et al.[22] and Mosinger.[23] Plasma glucose content was determined with a standard spectrophotometric method[24] using Cal Biochem Stat Pak Kit no. 86924. Plasma epinephrine and l-norepinephrine contents were measured with a modified method of Häggendal,[25] using dithiothreitol instead of dimercaptopropanol as the stabilizer for lutine fluorescence. At the time of this study the coefficients of variation of duplicate determinations were as follows: plasma lactate content 2.8 percent (no. = 60); pyruvate content 3.0 percent (no. = 60); free fatty acid content 1.9 percent (no. = 26); glucose content 1.4 percent (no. = 40); oxygen content 0.81 percent (no. = 26); carbon dioxide content 1.09 percent (no. = 26), epinephrine and l-norepinephrine contents 12.5 percent (no. = 25).

Cardiac output was measured in duplicate with the indocyanine green dilution technique.[26] The coefficient of variation of duplicate determinations in 35 patients with acute myocardial infarction was 4.2 percent. Coronary blood flow was measured with a modification of the method of Krasnow et al.,[27] using Iodine-125–labeled antipyrine as the indicator; details about the modification of the method and reproducibility were previously published.[19]

Metabolic classification: Data from each of the 173 metabolic studies were reduced by assignment to one of four classes based on arbitrarily defined metabolic patterns: normal, carbohydrate, free fatty acid and breakdown. Similar attempts at data reduction were made by Killip and Kimball,[29] using clinical observations, and by Forrester et al.,[30] using hemodynamic measurements. The metabolic classes were derived from previous metabolic studies[28] in patients without heart disease and in others with uncomplicated or complicated acute myocardial infarction. Myocardial lactate extraction values were used to define all four categories; myocardial free fatty acid extraction ratios were used in the case of free fatty acid and breakdown states. An additional criterion, the concentration of plasma free fatty acids, was used to define the free fatty acid state. Arterial glucose and pyruvate contents and myocardial extraction ratios of glucose and pyruvate were not considered for purposes of classification.

A metabolic state was defined as *normal* when myocardial lactate extraction ratios ranged between 15 and 30 percent, a range representing about ±2 standard deviations of the mean lactate extraction ratio observed in 20 previously studied normal persons (24 percent ± 8.30).[28] A *carbohydrate* state was defined as one in which myocardial lactate extraction exceeded 30 percent. A *free fatty acid* state was defined as one in which the arterial free fatty acid content exceeded 800 μmol/liter when the myocardial extraction ratio of free fatty acids equaled or exceeded 10 percent and the lactate extraction ratio was below 15 percent. A plasma free fatty acid concentration above 800 μmol/liter is comparable with values previously observed by us[31] and others[6,8,32] in acute myocardial infarction in man. The average plasma free fatty acid content of 456 μmol/liter ±105, obtained in our laboratory in 23 normal volunteers in the fasting state, is comparable with results reported by other investigators.[33–35] A metabolic *breakdown* state was defined as one in which the myocardial

TABLE I

Initial Hemodynamic and Cardiac Metabolic Data (mean ± standard deviation)

Metabolic Pattern	Stroke Index (ml/beat per m^2)	Heart Rate (beats/min)	Systemic Vascular Resistance (dynes sec cm^{-5})	Pulmonary Wedge Pressure (mm Hg)	Coronary Blood Flow (ml/100 g per min)	MVO_2 (ml/100 g per min)	Plasma Creatine Kinase (U/liter)
Normal + carbohydrate (no. = 14)	33.3 ± 5.9	76 ± 14	1411 ± 338	11.0 ± 1.7	84.5 ± 12.4	9.66 ± 2.66	983 ± 552
Free fatty acid (no. = 26)	34.7 ± 6.6	79 ± 22	1616 ± 445	14.1 ± 3.6	93.4 ± 9.8	11.59 ± 1.67	1242 ± 407
Breakdown (no. = 10)	23.8 ± 6.6	86 ± 12	2032 ± 589	17.8 ± 5.0	76.3 ± 10.0	9.42 ± 2.10	1530 ± 372
Probability (*P*) values							
NC-FFA	NS	NS	NS	<0.01	NS	<0.01	NS
NC-BKD	<0.001	NS	<0.001	<0.001	NS	NS	<0.01
FFA-BKD	<0.001	NS	=0.02	<0.001	<0.001	<0.01	=0.02

BKD = breakdown; FFA = free fatty acid; MVO_2 = myocardial oxygen consumption; NC = normal + carbohydrate; NS = not significant.

extraction ratio of lactate was less than 15 percent and that of free fatty acids was less than 10 percent.

Methods of statistical evaluation; calculation of derived data: Data were analyzed with standard statistical techniques using an IBM 1800 computer. Errors of experimental methods were expressed as the coefficient of variation. All results were initially evaluated in a multiple regression program for study of interrelations. Significance of change in any measured or calculated variable was tested with variance analysis.

Calculations of derived data was made as follows: Myocardial oxygen consumption (MVO_2, ml/100 g per min) = arterial-coronary sinus oxygen content difference times coronary blood flow. Myocardial extraction ratio (Ex, percent) = arterial-coronary sinus content difference divided by arterial content. Myocardial respiratory quotient = coronary sinus-arterial carbon dioxide content difference divided by arterial-coronary sinus oxygen content difference.

Results

Fifty patients with acute myocardial infarction were studied; 44 were men and 6 women. The age averaged 56 years (range 37 to 75). The site of acute infarction was anterior in 24 instances, anterolateral in 9, inferior in 14 and inferoposterior in 3. Seven of the 50 patients died in the hospital, 5 with shock and 2 with severe left ventricular failure. None of the patients had diabetes mellitus or increased plasma ketone bodies.

The first 12 hours: Twenty-six of the 50 patients exhibited the *free fatty acid pattern* on initial study; 10 patients presented with the *breakdown pattern*, 5 with the *carbohydrate pattern* and 9 presented with patterns of myocardial substrate extraction that were within normal limits.

Anterior and anterolateral wall infarctions were seen in 65 percent of patients with the free fatty acid pattern, in 90 percent of those with the breakdown pattern and in 50 percent of those with the normal and carbohydrate patterns.

Mean values for hemodynamic function, myocardial perfusion and oxygen consumption and for plasma enzymes are shown in Table I. Normal and carbohydrate patterns were considered a single group because of the small numbers. Left ventricular function was significantly more impaired in the metabolic breakdown group than in the other groups, as demonstrated by differences in stroke index, pulmonary capillary wedge pressure and systemic vascular resistance. Figure 1 shows that the variations of stroke index and pulmonary arterial wedge pressure within the free fatty acid group was much greater than in the combined normal-carbohydrate group. Myocardial oxygen consumption (Table I) was highest in the free fatty acid group (mean 11.59 ml/100 g per min) and differed significantly from that obtained in the normal-carbohydrate group. Coronary blood flow averaged 93 ml/100 g per min in the free fatty

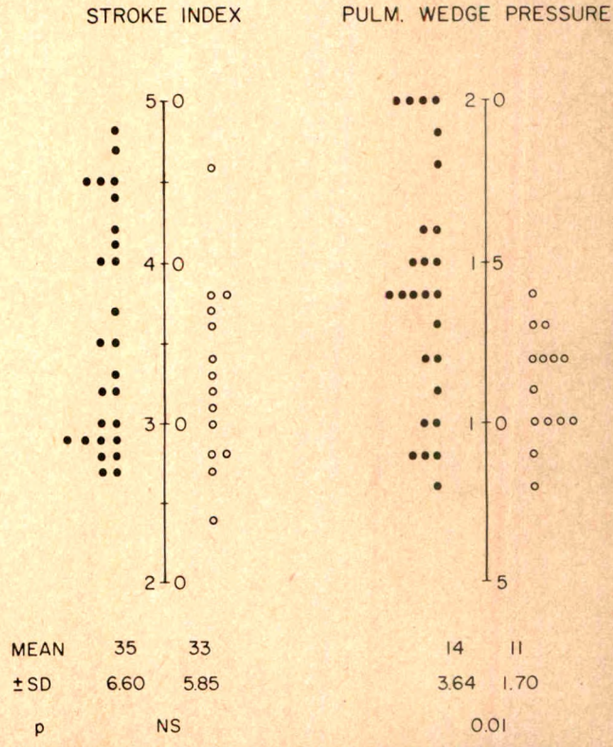

FIGURE 1. Initial values for stroke index (ml/beat per m^2) and pulmonary (PULM.) wedge pressure (mm Hg) in the free fatty acid group **(closed circles)** and combined normal-carbohydrate-group **(open circles).** Variation in the two measurements is greater in the former group. NS = not significant; p = probability; SD = standard deviation.

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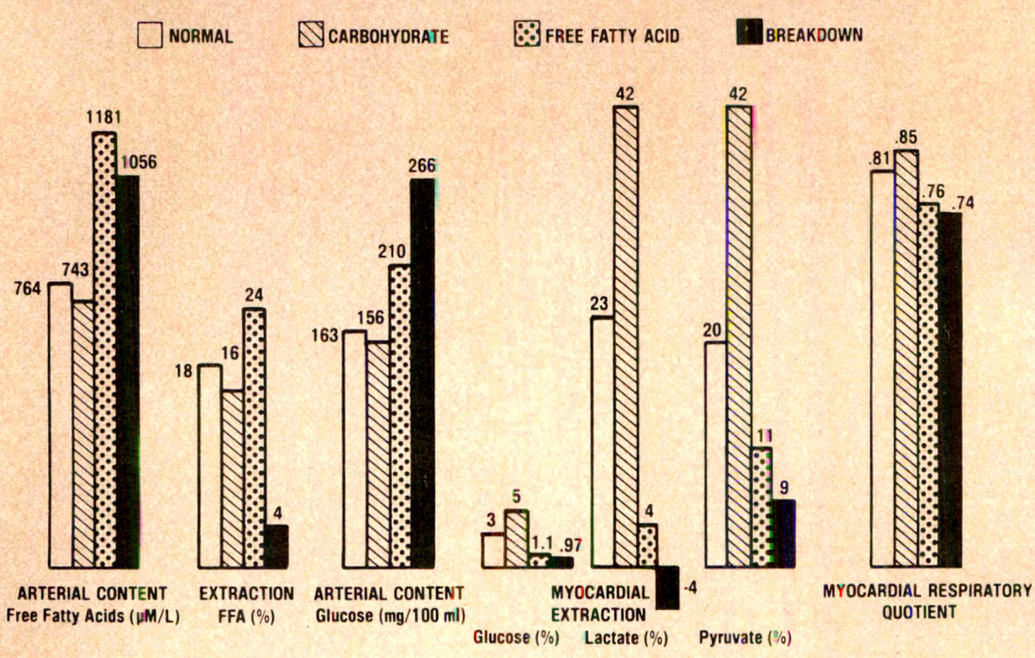

COMPARISON	p VALUES FOR t TEST						
N-CHO	NS	NS	NS	NS	--*	<.001	<.001
N-FFA	<.001	<.05	<.001	<.05	--	~.05	<.01
N-BKD	<.001	<.001	<.001	<.05	--	<.05	<.01
CHO-FFA	<.001	<.05	<.001	<.01	--	<.001	<.001
CHO-BKD	<.01	<.001	<.001	<.001	--	<.001	<.001
FFA-BKD	NS	--*	<.001	NS	--	NS	NS

FIGURE 2. Mean values of metabolic measurements for each of the four groups (173 studies). The free fatty acid (FFA) group had high arterial levels of free fatty acid (μmol/liter [μM/L]) and glucose, high myocardial extraction ratio of free fatty acids but low extraction ratios of glucose, lactate and pyruvate and a low myocardial respiratory quotient. In contrast, the normal (N) and carbohydrate (CHO) groups had lower arterial levels of both free fatty acids and glucose but higher extraction ratios of carbohydrates and higher myocardial respiratory quotients. The breakdown (BKD) group had high arterial substrate levels but low myocardial extraction ratios. (--*) = measurements defining groups are not included in statistical evaluation.

acid group and was significantly higher than in the breakdown group. Plasma peak creatine kinase was highest in the breakdown group, intermediate in the free fatty acid and lowest in the normal-carbohydrate group.

Sequential studies: Metabolic data from the 173 separate studies in the 50 patients are shown in Figure 2. Plasma glucose concentration, myocardial ratios for glucose and pyruvate extraction and for lactate production, and the myocardial respiratory quotient were not used as criteria for classification; plasma free fatty acid contents were not used except for definition of the free fatty acid group.

Plasma glucose contents were significantly higher and myocardial extraction ratios significantly lower in the free fatty acid and breakdown groups than in the carbohydrate and normal groups. Figure 3 shows that glucose extraction by the myocardium was impaired at high plasma glucose content levels; most patients with increased plasma glucose exhibited the free fatty acid or breakdown metabolic patterns.

Plasma lactate and pyruvate contents were within normal limits or slightly elevated in the four metabolic groups. They ranged between 1.35 and 1.87 mmol/liter for lactate and between 0.062 and 0.15 mmol/liter for pyruvate, respectively. They did not show significant differences among each other. Myocardial pyruvate extraction ratios (Fig. 2), not used for classification, showed a pattern similar to that for lactate extraction ratios. Most studies in the breakdown group exhibited lactate production.

Arterial free fatty acid concentrations were markedly elevated in both the free fatty acid and breakdown groups, and were significantly different from the lower contents in the carbohydrate and normal groups. Figure 4 demonstrates that plasma free fatty acid content and myocardial free fatty acid extraction were correlated ($r = 0.47$, $P < 0.001$). Free fatty acid extraction was lower in the normal and carbohydrate groups than in the free fatty acid group.

The myocardial respiratory quotient (Fig. 2) averaged 0.76 in the free fatty acid group, a value significantly different from the means of 0.81 and 0.85 in the normal and carbohydrate groups.

Heart rate and systolic/diastolic arterial pressures averaged 85 beats/min and 123/72 mm Hg, respectively,

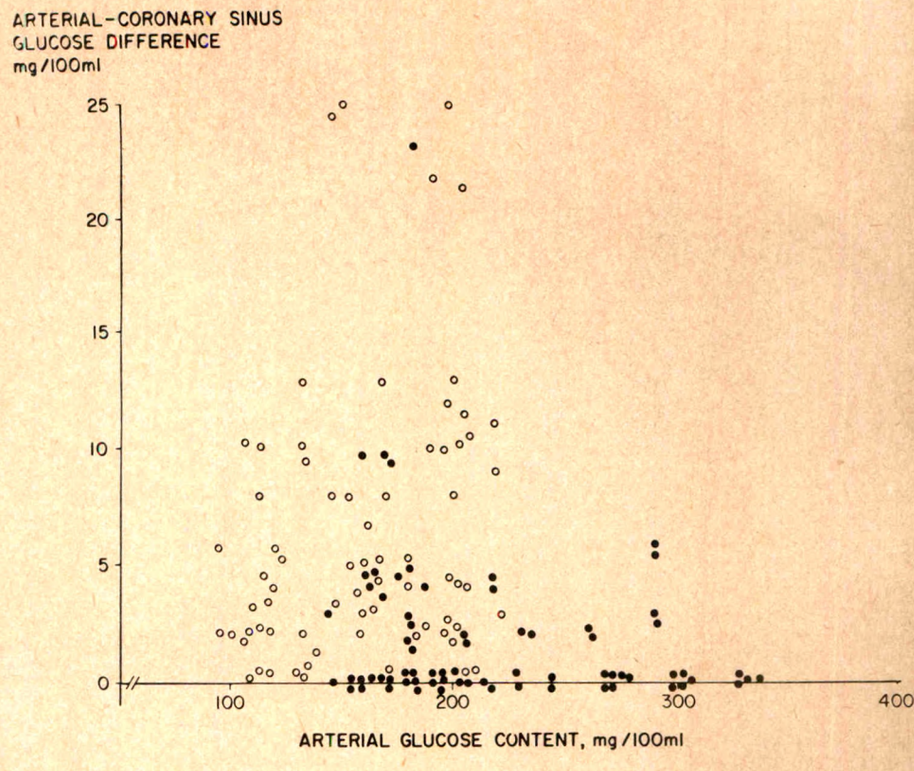

FIGURE 3. Myocardial glucose extraction ratios plotted as coordinates. Glucose extraction is low in the free fatty acid group **(closed circles)** in spite of high plasma glucose content. **Open circles** indicate combined normal-carbohydrate group.

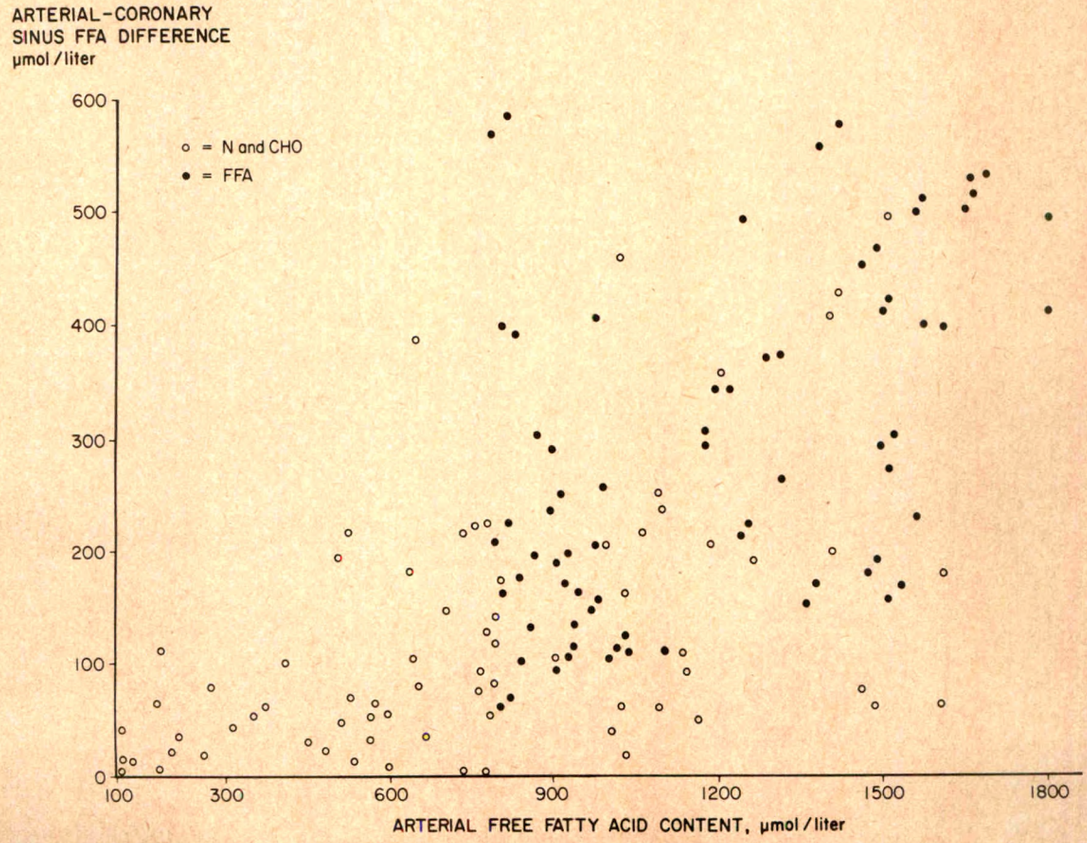

FIGURE 4. Myocardial free fatty acid extraction ratios plotted as coordinates. Plasma content and myocardial extraction are correlated ($r = 0.47$, $P < 0.001$). Free fatty acid extraction is higher in the free fatty acid group **(closed circles)** than in the combined normal-carbohydrate group **(open circles).**

TABLE II

Plasma Catecholamine Contents in Acute Myocardial Infarction (mean ± standard deviation)

Metabolic Pattern	Epinephrine* (μg/liter)	l-norepinephrine* (μg/liter)
Normal + carbohydrate (no. = 12)	1.32 ± 0.52	2.18 ± 0.54
Free fatty acid (no. = 8)	4.02 ± 1.33	5.30 ± 1.22
Breakdown (no. = 8)	8.32 ± 0.99	12.08 ± 2.30
Probability (*P*) values		
NC-FFA	<0.001	<0.001
NC-BKD	<0.001	<0.001
FFA-BKD	<0.001	<0.001

* Normal values in our laboratory (no. = 12): epinephrine 0.25 ± 0.14, l-norepinephrine 0.52 ± 0.26.
BKD = breakdown; FFA = free fatty acid; NC = normal + carbohydrate.

for the normal group, 88 beats/min and 125/73 mm Hg for the carbohydrate group and 84 beats/min and 127/73 mm Hg for the free fatty acid group. Significant differences in these measurements were not observed among these three groups. Heart rate and arterial pressures averaged 94 beats/min and 108/62 mm Hg in the breakdown group and were significantly different from values in the three other groups.

Plasma epinephrine and l-norepinephrine contents, measured in a limited number of patients, were highest in the breakdown group (Table II), intermediate in the free fatty acid and lowest in the normal-carbohydrate group.

Change from one metabolic state to another: During the sequential studies considerable change from one metabolic pattern to another was observed in the individual patients. Among those with the free fatty acid pattern, the state observed most frequently, the pattern changed to normal in 23 percent and to the breakdown state in 20 percent. Among those with the normal metabolic pattern, change to the free fatty acid and carbohydrate states occurred in 25 and 30 percent, respectively. Among those with the breakdown pattern the pattern changed to the free fatty acid state in 52 percent. In contrast, the carbohydrate pattern was relatively stable; it rarely changed to another metabolic state.

Clinical correlations: Figure 5 shows the clinical correlates to the metabolic findings at the time or within 1/2 hour of each of the 173 separate studies. One or more clinical complications were observed in 61 percent of the studies. More than half of the studies, performed during or close to the occurrence of ventricular arrhythmias, chest pain, extension of infarction or heart failure, exhibited the free fatty acid state; this metabolic pattern was seen in only 5 percent of the studies without evidence of clinical complications. Chi square analysis indicated that these differences were statistically significant ($P < 0.05$).

Effect of propranolol: Propranolol, 0.1 mg/kg body weight, was administered intravenously to 20 patients; the shift in substrate utilization produced is shown in Figure 6. The myocardial respiratory quotient increased from an average of 0.79 to 0.88. Five patients demonstrating the breakdown pattern and six patients demonstrating the free fatty acid pattern before propranolol administration shifted to a normal or carbohydrate

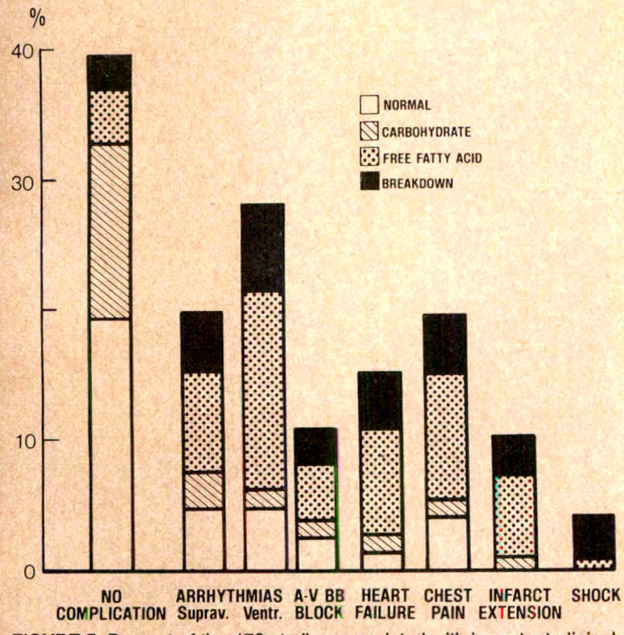

FIGURE 5. Percent of the 173 studies associated with important clinical complications. Complications did not occur in 39 percent of the studies (column 1). One or more complications are observed in the remaining studies (columns 2 to 8). More than half of the studies performed during or close to occurrence of ventricular (Ventr.) arrhythmias, chest pain, extension of infarction, or heart failure exhibit the free fatty acid state **(dotted areas).** This metabolic pattern was seen in only 5 percent of the studies without complications. A-V = atrioventricular; BB = bundle branch; Suprav. = supraventricular.

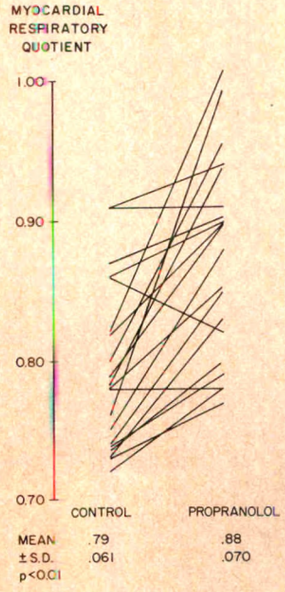

FIGURE 6. Effect of propranolol on myocardial respiratory quotient in 20 patients. Patients with the lowest myocardial respiratory quotient had the greatest change in substrate utilization with propranolol. p = probability; S.D. = standard deviation.

pattern. In these 11 patients plasma free fatty acid concentrations decreased from an average of 1,116 to 919 μmol/liter (P <0.05). Lactate production, present in 6 of the 11 patients, shifted to lactate extraction in all patients; the mean extraction ratio changed from 2.4 to 17 percent (P <0.01). Glucose extraction ratios increased from 0 to 4.9 percent (P <0.05). Free fatty acid extraction ratios did not significantly change; they averaged 15 percent before and after propranolol administration.

In the entire group of 20 patients propranolol decreased coronary blood flow from an average of 81 to 71 ml/100 g per min (P <0.001) and myocardial oxygen consumption from 9.8 to 7.1 ml/100 g per min (P <0.001). The arterial-coronary sinus oxygen difference decreased in 18 patients and remained unchanged in 2 patients. The decrease for the group averaged 0.81 ml/100 ml (P <0.001).

Discussion

The systemic response to myocardial infarction enhances sympathetic activity in particular, increases myocardial energy requirements and changes substrate patterns. Catecholamines are released into the circulation and myocardium[6,36–38]; plasma free fatty acids and glucose are increased[1–7] and abnormal glucose tolerance is observed.[1–4,6]

Our observations demonstrated that 71 of 173 studies, performed in 50 patients during the early phase of myocardial infarction, exhibited a pattern of predominant myocardial free fatty acid uptake. Because free fatty acid uptake rapidly decreases and ceases in acutely ischemic tissue,[39] coronary sinus blood was probably largely composed of venous efflux from the noninfarcted myocardial regions and the results reflect the response of relatively normal myocardium to acute stress. Thirty-five of the 173 studies exhibited enhanced carbohydrate uptake with lower plasma glucose and free fatty acid levels than in the free fatty acid group; 36 other studies showed normal metabolic findings with plasma levels similar to those with enhanced carbohydrate extraction. In 31 studies, obtained in patients who did not have shock but had significantly decreased hemodynamic function (Table I), free fatty acid concentrations were similar and glucose concentrations even higher than values in the patients exhibiting the free fatty acid pattern. Coronary sinus efflux probably largely reflects ischemic zone events in these studies because both myocardial glucose and free fatty acid extraction ratios were low and myocardial lactate production was present (breakdown group). Plasma l-norepinephrine and epinephrine contents, elevated in all studies, were substantially higher in this metabolic group (Table II).

Interactions between glucose and free fatty acid metabolism: These were described in 1963 by Randle et al.,[18] who presented evidence that carbohydrate intolerance in some situations is due to high plasma levels of free fatty acids and ketone bodies. They suggested that these interactions be considered a glucose-free fatty acid cycle. Lebovitz et al.[3] and Christensen and Videbaek[6] concluded that glucose intolerance in acute myocardial infarction was due to catecholamine-stimulated glycogenolysis coupled with inhibition of insulin release. The latter group observed that plasma glucose and free fatty acid concentrations were related to both plasma l-norepinephrine and basal insulin concentrations. A similar systemic hyperglycemic response has been observed in patients with nonischemic cardiovascular disease[40] and in patients undergoing exercise[41–43] or psychologic stress.[44] It probably represents a nonspecific stress syndrome.

Free fatty acid availability and role of stress-mediated catecholamine release: The importance of free fatty acids to myocardial function was shown by Neeley and co-workers[45,46] studying the isolated perfused rat heart. They demonstrated that, at physiologic concentrations, free fatty acids are oxidized in preference to carbohydrates at high and low levels of ventricular work. When glucose was the only available substrate, increased work levels led to a decrease in myocardial high energy phosphates; this decrease was reversed when free fatty acids were available. It appeared that glycolysis was unable to supply enough carbon substrate for the high rate of electron transport required by the stressed heart.

Stress-mediated catecholamine release increases both ventricular work and free fatty acid availability, evoking an integrated mechanical and substrate response to stress. This adaptation may have undesirable consequences in patients with acute myocardial infarction. Our data indicate that patients with high plasma catecholamine and free fatty acid contents, with increased myocardial free fatty acid uptake, and lowered myocardial respiratory quotient had more complications than those with predominant carbohydrate or normal metabolic patterns. Similar relations have been observed by other investigators.[9,10,33,47,48]

While the high complication rate in these patients may be directly related to catecholamine effects, Oliver et al.[13,14,49] have favored the view that increases in free fatty acid concentration may also exert independent effects. Free fatty acids have been shown to increase oxygen consumption by the heart[50–52]; blockade of catecholamine-stimulated lipolysis with beta-pyridylcarbinol substantially reduced myocardial oxygen consumption.[52] Inhibition of lipolysis reduced infarct size and degree of ischemia in experimental infarction.[52–54]

Instability of myocardial metabolic pattern in acute myocardial infarction: Our results demonstrate that the free fatty acid pattern observed in almost 50 percent of the metabolic studies was unstable. In many studies, plasma free fatty acid and glucose contents spontaneously decreased with resultant increases in carbohydrate extraction. However, in other studies, plasma free fatty acid and glucose concentrations remained high, but free fatty acid and carbohydrate extractions both were reduced as the myocardium released lactate. This frequent transition of the free fatty acid pattern to improved or deteriorating myocardial metabolism emphasizes the dynamic nature of myocardial

energy production in the early stages of acute myocardial infarction and may explain metabolic processes leading to extension of myocardial damage. Areas of biochemically normal tissue, contracting vigorously but perfused by an abnormal coronary vascular bed, presumably set the stage for extension of ischemia as areas of ischemic tissue set the stage for extension of necrosis.

Effect of propranolol on myocardial metabolic patterns: Relieving catecholamine stress by beta adrenergic blockade corrects the free fatty acid pattern and leads to better myocardial utilization of carbohydrates. The myocardial respiratory quotient increased from 0.79 to 0.88 indicating decreased utilization of free fatty acids by the myocardium. Opie et al.[55] made similar observations in experimental myocardial infarction. Propranolol decreased arterial content and myocardial extraction ratio of free fatty acids, while myocardial glucose extraction increased. Propranolol reduced free fatty acid uptake by the l-norepinephrine-stressed myocardium of the dog without changes in plasma free fatty acids, suggesting an adrenergic mechanism for regulation of free fatty acid uptake.[56] Myocardial extraction and arterial-coronary sinus difference of free fatty acids decreased with propranolol, whereas utilization of carbohydrates did not change.[57]

The mechanism by which propranolol promotes myocardial glucose utilization is unclear. Beta adrenergic blockade of pancreatic islet cells might be expected to increase rather than decrease carbohydrate intolerance. However, Ettinger et al.[40] did not observe increased glucose intolerance after administration of propranolol to patients with nonischemic heart disease even though glucose-stimulated insulin concentrations were less than before administration of propranolol. Several effects of propranolol may contribute to the substrate changes of the myocardium observed by us. Blockade of catecholamine stimulated lipolysis reduced plasma free fatty acid content, thereby diminishing myocardial uptake of free fatty acids. The resultant decline of mitochondrial citrate accumulation relieves inhibition of phosphofructokinase, a major control point for glycolysis.[58,59] Propranolol-mediated decreases in myocardial oxygen consumption may also diminish myocardial free fatty acid utilization by reducing the fluxes of free fatty acids needed for the accelerated electron transport required for the stressed heart. Furthermore, propranolol may reduce triglyceride turnover in the cytoplasm of the myocardial cell, reducing the pool of two carbon fragments presented to the tricarboxylic cycle for oxidative metabolism.

Clinical implications: These studies emphasize the relations among metabolic, hemodynamic and clinical phenomena in acute myocardial infarction. As the volume of infarcted tissue increases, ventricular performance declines, coronary sinus blood reveals increased evidence of anaerobic metabolism and clinical findings of pulmonary venous congestion and peripheral hypoperfusion are observed. The frequent occurrence of a systemic stress response modifies ventricular function; some patients maintain a relatively normal cardiac output in the face of substantial necrosis; others reveal hypoperfusion suggesting either less sympathetic stimulation or large volumes of necrosis. Treatment should be related to pathophysiologic abnormalities. Because salvage of endangered myocardium has a major priority, dampening of sympathetic response by beta adrenergic blockade appears promising for most patients without evidence of significant ventricular failure.

References

1. **Reaven G, Calciano A, Cody R, et al:** Carbohydrate intolerance and hyperlipemia in patients with myocardial infarction without known diabetes mellitus. J Clin Endocrinol 23:1013–1023, 1963
2. **Allison SP, Chamberlain MJ, Hinton P:** Intravenous glucose tolerance, insulin, glucose, and free fatty acid levels after myocardial infarction. Br Med J 4:776–778, 1969
3. **Lebovitz HE, Shultz KT, Matthews ME, et al:** Acute metabolic responses to myocardial infarction. Circulation 39:171–181, 1969
4. **Taylor SH, Saxton C, Majid PA, et al:** Insulin secretion following myocardial infarction. Lancet 2:1373–1377, 1969
5. **Kurt TL, Genton E, Chidsey C III, et al:** Carbohydrate metabolism and acute myocardial infarction: circulating glucose, insulin, cortisol and growth hormone responses and excretion of catecholamines. Chest 64:21–25, 1973
6. **Christensen NJ, Videbaek J:** Plasma catecholamines and carbohydrate metabolism in patients with acute myocardial infarction. J Clin Invest 54:278–286, 1974
7. **Opie LH:** Metabolism of free fatty acids, glucose and catecholamines in acute myocardial infarction. Am J Cardiol 36:938–953, 1975
8. **Kurien VA, Oliver MF:** Serum-free-fatty-acids after acute myocardial infarction and cerebral vascular occlusion. Lancet 2: 122–127, 1966
9. **Gupta DK, Young R, Jewitt DE, et al:** Increased plasma-free-fatty acid concentrations and their significance in patients with acute myocardial infarction. Lancet 2:1209–1213, 1969
10. **Rutenberg HL, Pamintuan JC, Soloff LA:** Serum-free-fatty-acids and their relation to complications after acute myocardial infarction. Lancet 2:559–564, 1969.
11. **Hagenfeldt L, Wester PO:** Plasma levels of individual free fatty acids in patients with acute myocardial infarction. Acta Med Scand 194:357–362, 1973
12. **Raab W, Van Lith P, Lepeschkin E, et al:** Catecholamine-induced myocardial hypoxia in the presence of impaired coronary dilatability independent of external cardiac work. Am J Cardiol 9:455–470, 1962
13. **Oliver MF, Kurien VA, Greenwood TW:** Relation between serum-free-fatty-acid and arrhythmias and death after acute myocardial infarction. Lancet 1:710–715, 1968
14. **Oliver MF:** Metabolic response during impending myocardial infarction. II. Clinical implications. Circulation 45:491–500, 1972
15. **Bing RJ, Vandam LD, Gregoire F, et al:** Catheterization of the coronary sinus and middle cardiac vein in man. Proc Soc Exp Biol Med 66:239–240, 1947
16. **Bing RJ, Siegel A, Vitale A, et al:** Metabolic studies on the human heart in vivo. Am J Med 15:284–296, 1953
17. **Bing RJ, Siegel A, Ungar I, et al:** Metabolism of the human heart. II. Studies on fat, ketone and amino acid metabolism. Am J Med 16:504–515, 1954
18. **Randle PJ, Garland PB, Hales CN, et al:** The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1:785–789, 1963
19. **Mueller H, Ayres SM, Gregory JJ, et al:** Hemodynamics, coronary

blood flow, and myocardial metabolism in coronary shock. Response to l-norepinephrine and isoproterenol. J Clin Invest 49: 1885–1902, 1970
20. **Van Slyke DD, Neill JM:** The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. Int J Biol Chem 61:523–573, 1924
21. **Dole VP:** A relation between non-esterified fatty acids in plasma and the metabolism glucose. J Clin Invest 35:150–154, 1956
22. **Trout DL, Estes EH Jr, Freidberg SJ:** Titration of free fatty acids of plasma: a study of current methods and a new modification. J Lipid Res 1:199–202, 1960
23. **Mosinger F:** Photometric adaptation of Dole's micro-determination of free fatty acids. J Lipid Res 6:157–159, 1965
24. **Kornberg A, Horecker BL:** Glucose-6-phosphate dehydrogenase. In, Methods of Enzymology (Colowick P, Kaplan NO, ed). New York, Academic Press, 1955, p 323–324
25. **Häggendal J:** An improved method for fluorimetric determination of small amounts of adrenaline and noradrenaline in plasma and tissues. Acta Physiol Scand 59:242–254, 1963
26. **Hamilton WF, Moore JW, Kinsman JM, et al:** Studies on the circulation. IV. Further analysis of the injection method, and of changes in hemodynamics under physiological and pathological conditions. Am J Physiol 99:534–551, 1932
27. **Krasnow N, Levine HJ, Wagman RJ, et al:** Coronary blood flow measured by I^{131} iodoantipyrine. Circ Res 12:58–62, 1963
28. **Mueller H, Ayres SM:** Myocardial metabolism in shock following acute myocardial infarction. In, Shock in Myocardial Infarction (Gunnar RM, Loeb HS, Rahimtoola SH, ed). New York, Grune & Stratton, 1974, p 173–207
29. **Killip T, Kimball JT:** Treatment of myocardial infarction in a coronary care unit. Am J Cardiol 20:457–464, 1967
30. **Forrester JS, Diamond G, Chatterjee K, et al:** Medical therapy of acute myocardial infarction by application of hemodynamic subsets. N Engl J Med 295:1356–1362; 1404–1415, 1976
31. **Mueller HS, Ayres SM, Religa A, et al:** Propranolol in the treatment of acute myocardial infarction. Effect on myocardial oxygenation and hemodynamics. Circulation 49:1078–1087, 1974
32. **Russell RO Jr, Rogers WJ, Mantle JA, et al:** Glucose-insulin-potassium, free fatty acids and acute myocardial infarction in man. Circulation 53, 54: Suppl I:I-207–I-209, 1976
33. **Falholt K, Lund B, Falholt W:** An easy colorimetric method for routine determination of free fatty acids in plasma. Clin Chim Acta 46:105–111, 1973
34. **Gerich JE, Langlois M, Schneider V, et al:** Effects of alterations of plasma free fatty acid levels on pancreatic glucagon secretion in man. J Clin Invest 53:1284–1289, 1974
35. **Rogers WJ, Russell RO Jr, Moraski RE, et al:** Effect of heparin-induced elevation of free fatty acids on myocardial oxygen consumption in man (abstr). Am J Cardiol 37:167, 1976
36. **Jewitt DE, Mercer CJ, Reid D, et al:** Free noradrenaline and adrenaline excretion in relation to the development of cardiac arrhythmias and heart failure in patients with acute myocardial infarction. Lancet 1:635–641, 1969
37. **Prakash R, Parmley WW, Horvat M, et al:** Serum cortisol, plasma free fatty acids and urinary catecholamines as indicators of complications in acute myocardial infarction. Circulation 45:736–745, 1972
38. **Wollenberger A, Krause EG, Shabab L:** Endogenous catecholamine mobilization and the shift to anaerobic energy production in the acutely ischemic myocardium. In, Coronary Circulation and Energetics of the Myocardium (Marchetti G, Taccardi B, ed). Basel, S Karger, 1967, p 200–219
39. **Weiss ES, Hoffman EJ, Phelps ME, et al:** External detection and visualization of myocardial ischemia with ^{11}C-substrates in vitro and in vivo. Circ Res 39:24–32, 1973
40. **Ettinger PO, Oldewurtel HA, Dzindzio B, et al:** Glucose intolerance in nonischemic cardiac disease. Role of cardiac output and adrenergic function. Circulation 43:809–823, 1971
41. **Nikkilä EA, Taskinen MR, Miettinen RA, et al:** Effect of muscular exercise on insulin secretion. Diabetes 17:209–218, 1968
42. **Sukkar MY, Hunter WM, Passmore R:** The effect of a protein meal with and without subsequent exercise on plasma insulin and growth hormone. J Exp Physiol 53:206–217, 1968
43. **Brisson GR, Malaisse-Lagae F, Malaisse WJ:** Effect of phentolamine upon insulin secretion during exercise. Diabetologia 7: 223–226, 1971
44. **Mason JW, Wool M, Wherry FE, et al:** Plasma growth hormone response to avoidance sessions in the monkey. Psychosom Med 30:760–773, 1968
45. **Neeley JR, Morgan HE:** Relationship between carbohydrate and lipid metabolism and energy balance of heart muscle. Am Rev Physiol 36:413–459, 1974
46. **Neeley JR, Whitmer KM, Mochizuki S:** Effects of mechanical activity and hormones on myocardial glucose and fatty acid utilization. Circ Res 38:Suppl I:I-22–I-30, 1976
47. **Maling HM, Moran NC:** Ventricular arrhythmias induced by sympathomimetic amines in unanesthetized dogs following coronary artery occlusion. Circ Res 5:409–413, 1957
48. **Januszewicz W, Sznajderman M, Ciswicka-Sznajderman M, et al:** Plasma free fatty acid and catecholamine levels in patients with acute myocardial infarction. Br Heart J 33:716–718, 1971
49. **Oliver MF, Rowe MJ, Luxton MR, et al:** Effect of reducing circulating free fatty acids on ventricular arrhythmias during myocardial infarction and on ST-segment depression during exercise-induced ischemia. Circulation 53, 54:Suppl I:I-210–I-212, 1976
50. **Challoner D, Steinberg D:** Effect of free fatty acid on the oxygen consumption of perfused rat heart. Am J Physiol 210:280–286, 1966
51. **Mjøs OD:** Effect of free fatty acids on myocardial function and oxygen consumption in intact dogs. J Clin Invest 50:1386–1389, 1971
52. **Mjøs OD, Kjekshus JK, Lekven J:** Importance of free fatty acids as a determinant of myocardial oxygen consumption and myocardial ischemic injury during norepinephrine infusion in dogs. J Clin Invest 53:1290–1299, 1974
53. **Kjekshus JK, Mjøs OD:** Effect of inhibition of lipolysis on infarct size after experimental coronary artery occlusion. J Clin Invest 52:1770–1778, 1973
54. **Mjøs OD, Miller NE, Riemersma RA, et al:** Effects of p-chlorophenoxyisobutyrate on myocardial free fatty acid extraction, ventricular blood flow, and epicardial ST-segment elevation during coronary occlusion in dogs. Circulation 53:494–500, 1976
55. **Opie LH, Thomas M:** Propranolol and experimental myocardial infarction: substrate effects. Postgrad Med J 52:Suppl 4:124–133, 1976
56. **Glaviano VV, Masters TN:** The effects of intracoronary norepinephrine on cardiac metabolism before and after beta adrenergic blockade (abstr). Fed Proc 26:771, 1967
57. **Marchetti G, Merlo L, Noseda V:** Myocardial uptake of free fatty acids and carbohydrates after beta adrenergic blockade. Am J Cardiol 22:370–374, 1968
58. **Passonneau JV, Lowry OH:** P-fructokinase and the control of the citric acid cycle. Biochem Biophys Res Comm 13:372–379, 1963
59. **Mansour TE:** Phosphofructokinase. Curr Top Cell Regul 5:1–46, 1972

Exercise Training and Plasma Catecholamines in Patients With Ischemic Heart Disease

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A 3 month program of exercise training was carried out in 10 patients with ischemic heart disease to assess the contribution of catecholamines to the training effect of improved exercise capacity and enhanced myocardial oxygen delivery. Training resulted in a significant increase in maximal treadmill exercise time (mean ± standard error of the mean 374 ± 28 versus 567 ± 33 seconds, $P < 0.0001$). The heart rate-arterial pressure product, an index of myocardial oxygen consumption, was decreased at rest and at all levels of exercise after training. After training, the mean plasma norepinephrine level during supine rest was reduced (320 ± 23 to 191 ± 20 pg/ml, $P < 0.01$) and plasma epinephrine values were unchanged. When these previously sedentary patients exercised on a treadmill to the maximal level attained before exercise training, the mean plasma norepinephrine and plasma epinephrine concentrations were significantly reduced. These data suggest that the beneficial adaptations of the cardiovascular system to exercise training are at least partially mediated by changes in the catecholamine response to exercise.

Physical training has been shown to improve exercise performance in patients with coronary artery disease and angina pectoris,[1–4] and epidemiologic data[5–7] have suggested that regular exercise is associated with a decreased incidence of sudden death or myocardial infarction, or both. Clinical investigations[4,8,9] of these beneficial effects have shown that, after exercise training, arterial blood pressure and heart rate are lower at any given work level; these reductions result in a decreased myocardial oxygen consumption and thus allow a patient to achieve a greater intensity of exercise before angina is felt. These physiologic adaptations to exercise training are similar to those resulting from the administration of beta adrenergic blocking drugs such as propranolol; thus, alteration in the sympathetic nervous system could be responsible for the improvement in exercise tolerance of patients with coronary artery disease after exercise training.[10,11] To evaluate this possibility, we measured the plasma catecholamines in patients with ischemic heart disease before and after a 3 month exercise training program.

Methods

Patients: Ten men, aged 40 to 55 years, were referred by their physician for participation in a cardiac rehabilitation program. All were working at the job they had held before their heart disease developed. Six patients reported that they have had exertional chest pain for 6 months to 2 years and were using sublingual nitroglycerin as necessary for relief of angina. Two patients were also taking propranolol, but during the study the drug was discontinued in one patient and the dose decreased (from 60 to 30 mg/day) in the other after a progressively worsening bradycardia developed. All other medications were unchanged during this study. Seven patients had had a myocardial infarction in the preceding 1 to 3 years, as documented by characteristic electrocardiographic and serum enzyme changes. Selective coronary angiography revealed the presence of sig-

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TABLE I

Hemodynamic Variables, S-T Depression and Maximal Treadmill Exercise Time Before and After Physical Training in 10 Patients (mean ± standard error of the mean)

Physical Condition	Heart Rate (beats/min)			S-T Area) (μv-sec)		Treadmill Time (sec)		HR × BP (×10³)		
	At Rest	Ex 1	Ex 2	Ex 1	Ex 2	Ex 1	Ex 2	At Rest	Ex 1	Ex 2
Sedentary	78 ± 4	139 ± 7	----	−13 ± 2	----	374 ± 28	----	9.7 ± 0.8	21.9 ± 1	----
Trained	69 ± 3	124 ± 6	154 ± 6	−9 ± 1	−14 ± 1	374 ± 28	567 ± 33	8.1 ± 0.5	16.8 ± 1	24.6 ± 1
P value	<0.003	<0.001	----	<0.01	----	----	----	<0.04	<0.002	----

Ex 1 = maximal treadmill time before training; Ex 2 = maximal treadmill time after training; HR × BP = heart rate-arterial systolic pressure product; NS = not significant; *P* = probability; S-T area = sum of all S-T segment depressions.

nificant coronary artery disease in six patients. Two patients had undergone coronary bypass surgery.

The patients continued their regular or fat-modified diet during the 3 month study, so that a relatively constant body weight was maintained. All patients had blood drawn for lipid profiles after a 12 hour fast. Five patients had a normal profile; four had hypercholesterolemia and one patient had hypertriglyceridemia.

Protocol: The patients reported in a fasting state to the exercise laboratory, where an indwelling intravenous needle was inserted into a left forearm vein. They then lay supine in a quiet room for 20 minutes, before a venous blood sample was drawn and a maximal treadmill exercise test using the Bruce protocol was performed.[12] Another venous blood sample was obtained on completion of the treadmill test. Three electrocardiographic leads (X, Y and Z or V_4, V_5 and V_6) were recorded on magnetic tape for 3 minutes at rest, during the exercise test and for 6 minutes after the exercise test. Arterial blood pressure was measured indirectly from the right brachial artery using a mercury syphygmomanometer and stethoscope. This pressure was measured at 3 minute intervals during and after exercise. The product of heart rate and systolic arterial pressure was calculated and used as an index of myocardial oxygen consumption.[13]

The treadmill test was stopped when angina pectoris developed, significant S-T segment changes were noted or the patient was unable to continue because of fatigue. The S-T segment changes were quantitated by measuring the deviation from the baseline level during the initial 80 msec from the J point.[14] This value is expressed in microvolts-sec (μv-sec), and values exceeding 10 μv-sec are abnormal, usually indicating myocardial ischemia.

Training program: The program consisted of three 50 minute exercise sessions per week for 12 weeks. Each of the 10 patients attended at least 28 of the 36 sessions. During the initial 20 minutes of each session the patients performed calisthenics; during the remaining 30 minutes they walked or jogged. Patients without angina exercised to 60 to 70 percent of their maximal heart rate. Patients with angina exercised to a heart rate that could be tolerated 1 to 5 minutes before angina was elicited. The electrocardiogram was monitored with use of telemetry and recorded on magnetic tape during the initial sessions and at monthly intervals. After 3 months of training, the treadmill exercise test was repeated to the duration of maximal exercise attained before training. After a 30 minute rest, a second treadmill test was performed to the patient's new maximal work level. Plasma for catecholamine determinations was obtained after supine rest and at the completion of each treadmill test.

Plasma catecholamines: Blood samples were drawn into a heparinized syringe and placed in iced tubes containing reduced glutathione (5 mmolar, Sigma) combined with heparin, 500 units/ml (FBA Pharmaceuticals). All tubes were promptly spun in a refrigerated centrifuge, and the supernatants frozen until the analyses were performed. Norepinephrine and epinephrine were measured in 250 microliters (μl) of plasma using the single isotope derivative method of Passon and Peuler[15] with only minor modifications.[16] In our laboratory, this method has a sensitivity of 10 to 20 picograms (pg) of norepinephrine and epinephrine and is highly reproducible with interassay coefficients of variation of less than 6 percent for epinephrine and norepinephrine in physiologic concentrations.[16]

A paired *t* test was used to evaluate the significance of changes in exercise performance, hemodynamic variables, electrocardiogram and plasma catecholamines.

Results

Heart rate and blood pressure: Nine patients had a reduced resting heart rate after the 3 month training period (Table I); blood pressure was unchanged in eight patients and decreased to normal levels in two mildly hypertensive patients. The one patient whose resting heart rate was increased stopped taking propranolol during the study. As a result of these changes, the heart rate-systolic arterial pressure product was decreased in 9 of the 10 patients at rest (Table I).

Before exercise training, these patients exercised an average of 374 ± 28 (mean ± standard error of the mean) seconds on the treadmill using the Bruce protocol for speed and elevation (Table I). After training, when they exercised to their previous maximal level, there was a significant reduction from the pretraining level in heart rate or blood pressure, or both, at the end of treadmill exercise, and the heart rate-blood pressure product, a measure of myocardial oxygen consumption, was significantly reduced. When these patients then exercised to their new maximal level, they had a mean treadmill exercise time of 567 ± 33 seconds, a 52 percent increase over their pretraining exercise time ($P < 0.0001$), and the maximal heart rate-blood pressure product attained was significantly greater ($P < 0.02$) than that attained before training (Table I).

Before exercise training, six patients stopped the treadmill test because of angina pectoris, whereas only

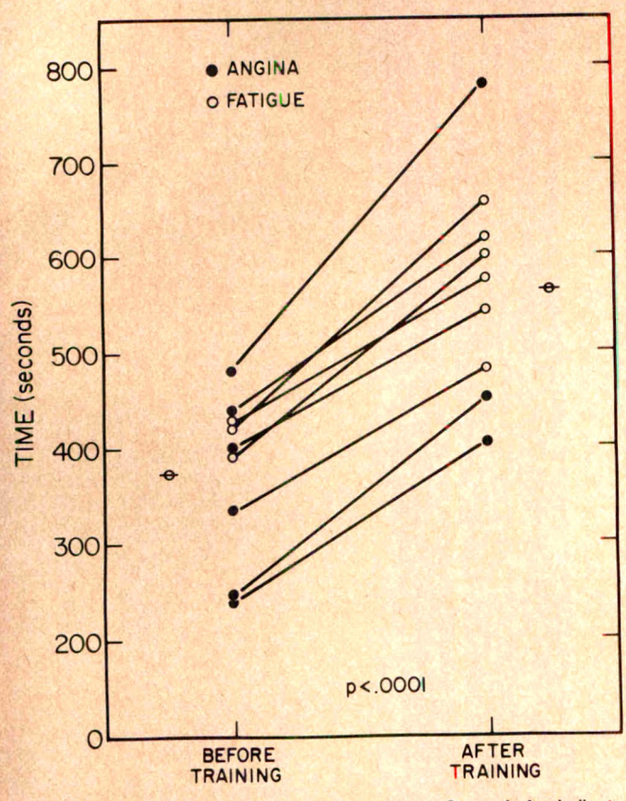

FIGURE 1. Effect of training on exercise capacity. **Open circles** indicate the time at which fatigue occurred, **closed circles,** the time at which angina occurred, and **barred circles** mean values. Time indicates the number of seconds of treadmill exercise using the Bruce protocol.[12] p = probability.

three of these patients noted angina with maximal exercise after training. The other patients stopped the treadmill test because of fatigue or breathlessness (Fig. 1). Three patients had frequent ventricular premature beats (more than 6 beats/min) during exercise before training but had no such beats after completion of the training program.

Plasma catecholamines: Catecholamine levels measured with patients in the resting supine position were 29 ± 5 pg/ml for epinephrine and 320 ± 23 pg/ml for norepinephrine (Table II). After 3 months of exercise training, resting plasma epinephrine values were unchanged, but plasma norepinephrine was significantly decreased in all patients, averaging 191 ± 20 pg/ml. In blood obtained at the end of the maximal treadmill exercise test before training, both plasma catecholamines were increased. After training, there was a significant reduction in plasma epinephrine (P <0.03) and norepinephrine (P <0.02) when patients exercised to their previous maximal level (Table II). When they exercised to their new increased maximal work capacity, plasma catecholamine levels were greater than those attained before exercise training.

Four patients (not included in this study) began the exercise program but were able to attend less than 50 percent of the sessions or voluntarily stopped attending the sessions. In this group, resting and exercise plasma catecholamines, heart rate, blood pressure and treadmill exercise time were unchanged after 3 months as compared with initial pretraining values. Three of these patients had ischemic heart disease; the fourth had a mitral valve prosthesis.

Electrocardiographic findings: In nine patients significant S-T segment depression (10 μv-sec or more) developed during the initial treadmill test. One patient with prior coronary bypass surgery had a normal S-T segment on treadmill testing. After training, seven patients had less S-T segment depression (P <0.01) when they exercised to their previous maximal level (Table I). Five patients now had a normal exercise test as defined by the S-T segment changes. When these trained patients now exercised to their maximal level, the degree of S-T segment depression was not significantly different from that before training, although both the duration of exercise and the heart rate-blood pressure product were significantly increased.

Discussion

Exercise training, exercise capacity and myocardial oxygen consumption: Our results confirm that a program of exercise training produces appreciable improvement in the exercise capacity of patients with coronary artery disease. In previous studies of the mechanisms of this improvement, the change was attributed to changes in the circulatory response to exercise that reduced the oxygen requirement of the heart at a given level of exercise.[1,2,4] Thus, the response of systolic arterial pressure and heart rate to a given level

TABLE II

Plasma Epinephrine and Norepinephrine in 10 Patients Before and After Physical Training (mean ± standard error of the mean)

Physical Condition	Epinephrine (pg/ml)			Norepinephrine (pg/ml)		
	Supine	Ex 1	Ex 2	Supine	Ex 1	Ex 2
Sedentary	29 ± 5	155 ± 15	-------	320 ± 23	2120 ± 77	-------
Trained	29 ± 5	61 ± 12	323.4 ± 23	191 ± 20	1007 ± 73	3003 ± 101
P value	NS	<0.03	-------	<0.01	<0.02	-------

Abbreviations as in Table I.

of exercise has been shown to be diminished.[1,2,4] Our study supports the conclusion that regular exercise training reduces the myocardial oxygen cost of a given exercise load, as reflected by a decreased heart rate-systolic arterial pressure product at a given level of exercise. Although myocardial oxygen consumption was not measured in our study, the heart rate-pressure product has been shown to be an accurate indicator of this physiologic need.[10,17]

After 3 months of exercise training, the maximal heart rate-systolic arterial pressure product attained with maximal treadmill exercise was increased in 6 of the 10 patients. If an increase in myocardial oxygen consumption can be inferred from this increase, our results suggest that physical training enhances myocardial oxygen delivery or decreases myocardial oxygen consumption at a given level of exercise in some patients with coronary artery disease.

Our study also demonstrated a reduction in the electrocardiographic S-T segment changes at a given level of exercise after training. If the amount of S-T segment depression or elevation reflects the degree of myocardial ischemia, these findings lend additional support to the hypothesis that exercise training reduces myocardial oxygen consumption or increases oxygen delivery at a given level of exercise. Although the number of patients (3 of 10) in our study with ventricular arrhythmias was too small to allow a significant evaluation of the effect of exercise training, no ventricular arrhythmias were detected in these patients after 3 months of training.

Exercise training and plasma catecholamines: Exercise training produces complex adaptations in both skeletal and cardiac muscle that are reflected in multiple hormonal, biochemical and anatomic alterations.[18,19] Epinephrine, primarily originating in the adrenal medulla, and norepinephrine, arising primarily from sympathetic postganglionic neurons, are essential for maintaining cardiovascular homeostasis because of their positive effects on three primary determinants of myocardial oxygen consumption—heart rate, blood pressure and myocardial contractility. After exercise training, we found a significant reduction in plasma norepinephrine during supine rest and a decrease in both plasma catecholamines at a given level of treadmill exercise. The catecholamine response to exercise and training in our patients with heart disease is similar to that reported in seven normal young adults.[19] These findings suggest that the adaptation of the cardiovascular system to exercise training is partially mediated by way of the sympathetic nervous system and is reflected by a reduced output of catecholamines at a given work level. Our data also suggest that sympathetic activity is better tolerated in trained patients, who are able to attain higher levels of maximal heart rate, blood pressure and plasma catecholamine concentration after regular exercise training. This has been suggested in other clinical studies[4,9] showing a larger heart rate-blood pressure product at the onset of angina pectoris after exercise training.

Since the introduction of sensitive biochemical methods for the estimation of physiologic changes in plasma catecholamines, several investigators[20,21] have noted that heavy exercise is associated with an increase in catecholamines. Haggendal[20] and Davies[21] and their co-workers showed that for a given form of exercise the increase in plasma catecholamines is more closely related to relative (expressed as percent of maximal oxygen consumption) than to absolute energy expenditure. Plasma catecholamine concentrations in normal persons are reported to increase only slightly at work levels that are less than 50 percent of maximal work but to increase curvilinearly at work levels exceeding 50 percent of maximum.[21,22] At low work levels the increased heart rate is probably due to a decrease in vagal tone, whereas at higher work levels increased sympathoadrenal function is also elicited with an increase in plasma catecholamine concentrations.[22] Pharmacologic studies[23] utilizing atropine and propranolol have reported similar conclusions.

Clinical implications: Previous experimental and clinical studies[24–26] have indicated that the sympathetic nervous system is intimately involved in the morbidity and mortality resulting from coronary artery disease. Stimulation of this system or the intravascular administration of catecholamines will produce serious ventricular arrhythmias and increase the myocardial necrosis in experimental animals.[24,25] The administration of beta adrenergic blocking agents reduces these ventricular arrhythmias and the amount of necrosis.[27,28] When these drugs are given to patients with angina pectoris, exercise tolerance is increased, with a reduction in heart rate and blood pressure at a given level of exercise,[11,29] and the electrocardiographic changes induced by exercise are diminished.[11] These findings with beta blocking agents are similar to those we found after exercise training. We suggest that the mechanism of improvement in our patients after exercise training is at least partially mediated by adaptations that result in a lower plasma catecholamine concentration at a given level of exercise and a better tolerance of the heart to catecholamines.

References

1. **Hanson JS, Tabakin BS, Levy AM, et al:** Long-term physical training and cardiovascular dynamics in middle-aged men. Circulation 38:783–799, 1968
2. **Clausen JP, Larsen OA, Trap-Jensen J:** Physical training in the management of coronary artery disease. Circulation 40:143–153, 1969
3. **Detry JM, Rousseau M, Vandenbroucke G, et al:** Increased arteriovenous oxygen difference after physical training in coronary heart disease. Circulation 44:109–118, 1971
4. **Redwood DR, Rosing DR, Epstein SE:** Circulatory and symptomatic effects of physical training in patients with coronary-artery disease and angina pectoris. N Engl J Med 286:959–965, 1972
5. **Paffenbarger RS, Laughlin ME, Gima AS, et al:** Work activity of longshoremen as related to death from coronary heart disease and

stroke. N Engl J Med 282:1109–1114, 1970
6. **Rechnitzer PA, Pickard HA, Paivs AV, et al:** Long-term follow-up study of survival and recurrence rates following myocardial infarction in exercising and control subjects. Circulation 45:853–857, 1972
7. **Morris JN, Adam C, Chave SPW, et al:** Vigorous exercise in leisure-time and the incidence of coronary heart-disease. Lancet 1:333–339, 1973
8. **Clausen JP:** Circulatory adjustments to dynamic exercise and effect of physical training in normal subjects and in patients with coronary artery disease. Prog Cardiovasc Dis 18:459–495, 1976
9. **Sim DN, Neill WA:** Investigation of the physiological basis for increased exercise threshold for angina pectoris. J Clin Invest 54: 763–770, 1974
10. **Jorgensen CR, Wang K, Wang Y, et al:** Effect of propranolol on myocardial oxygen consumption and its hemodynamic correlates during upright exercise. Circulation 48:1173–1182, 1973
11. **Dagenais GR, Moisan A, Marques Y:** Effects of practolol on exercise tolerance, cardiac hemodynamics, and metabolism in patients with coronary artery disease. Cardiovasc Res 10:25–36, 1976
12. **Bruce RA, Hornsten TR:** Exercise stress testing in evaluation of patients with ischemic heart disease. Prog Cardiovasc Dis 11: 371–390, 1969
13. **Nelson RR, Gobel FL, Jorgensen CR, et al:** Hemodynamic predictors of myocardial oxygen consumption during static and dynamic exercise. Circulation 50:1179–1189, 1974
14. **Sheffield LT, Holt JH, Lester FM, et al:** On-line analysis of the exercise electrocardiogram. Circulation 40:935–944, 1969
15. **Passon PG, Peuler JD:** A simplified radiometric assay for plasma norepinephrine and epinephrine. Anal Biochem 51:618–631, 1973
16. **Cryer PE, Santiago JV, Shah S:** Measurement of norepinephrine and epinephrine in small volumes of human plasma by a single isotope derivative method: response to the upright posture. J Clin Endocrinol Metab 39:1025–1029, 1974
17. **Kitamura K, Joegensen CR, Gobel FL, et al:** Hemodynamic correlates of myocardial oxygen consumption during upright exercise. J Appl Physiol 32:516–522, 1972
18. **Holloszy JO:** Adaptations of muscular tissue to training. Prog Cardiovasc Dis 18:445–458, 1976
19. **Hartley LH, Mason JW, Hogan RP, et al:** Multiple hormonal response to physical training. J Appl Physiol 33:602–606, 1972
20. **Haggendal J, Hartley LH, Salten B:** Arterial nor-adrenaline concentration during exercise in relation to relative work loads. Scand J Clin Lab Invest 26:337–342, 1970
21. **Davies CTM, Few J, Foster KG, et al:** Plasma catecholamine concentration during dynamic exercise involving different muscle groups. Eur J Appl Physiol 32:195–206, 1974
22. **Christensen NJ, Brandsborg O:** The relationship between plasma catecholamine concentration and pulse rate during exercise and standing. Eur J Clin Invest 3:299–306, 1973
23. **Epstein SE, Robinson BF, Kahler RL, et al:** Effects of beta adrenergic blockade on the cardiac response to maximal and submaximal exercise in man. J Clin Invest 44:1745–1753, 1965
24. **Maling HM, Moran NC:** Ventricular arrhythmias induced by sympathomimetic amines in unanesthetized dogs following coronary occlusion. Circ Res 5:409–413, 1957
25. **Verrier RL, Thompson PL, Lown B:** Ventricular vulnerability during sympathetic stimulation: role of heart rate and blood pressure. Cardiovasc Res 8:602–610, 1974
26. **Ceremuzynski L, Staszewska-Barczak J, Herboczynska-Cedro K:** Cardiac rhythm disturbances and the release of catecholamines after coronary occlusion in dogs. Cardiovasc Res 3:190–197, 1969
27. **Opie LH:** Metabolism of free fatty acids, glucose and catecholamines in acute myocardial infarction. Relation to myocardial ischemia and infarct size. Am J Cardiol 36:938–953, 1975
28. **Wilhelmsson C, Vedin JA, Wilhelmsen L, et al:** Reduction of sudden deaths after myocardial infarction by treatment with alprenolol. Lancet 2:1157–1160, 1974
29. **Wilson AG, Brooke OG, Lloyd HJ, et al:** Mechanism of action of beta-adrenergic receptor blocking agents in angina pectoris: comparison of action of propranolol with dextropropranolol and practolol. Br Med J 4:399–401, 1969

Slow Filling Period/Rapid Filling Period Ratio in the Apexcardiogram: Relation to the Diagnosis of Coronary Artery Disease

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Apexcardiograms were performed in 68 consecutive patients who had either normal findings or coronary artery disease on cardiac catheterization. The height of the *a* wave in relation to the total apexcardiographic deflection (a/H) and the duration of both the rapid (RFW) and the slow (SFW) filling periods were determined in each case. The patients were classified into three groups: I, no evidence of heart disease on catheterization; II, significant coronary artery disease with elevated left ventricular end-diastolic pressure; and III, coronary artery disease with normal filling pressure. There was a significant difference ($P < 0.001$) between the SFW/RFW values (mean ± 1 standard deviation) in control subjects (group I, 2.3 ± 0.5) and in subjects with coronary artery disease (group II, 4.7 ± 1.6 and group III, 4 ± 1.7). Setting the upper limit of normal for SFW/RFW at 2.8 (mean + 1 standard deviation) identified 94 percent of patients in group II, 71 percent of patients in group III and 86 percent of all patients with coronary disease (group II plus group III). This sensitivity appeared greater than that of the a/H ratio. Only 2 of 17 patients (12 percent) without coronary atherosclerosis had an SFW/RFW ratio greater than 2.8. It is concluded that (1) the slow/rapid filling period ratio is a useful noninvasive measurement for identifying subjects with ischemic heart disease; (2) the increased values for slow/rapid filling period ratio associated with obstructive coronary lesions may be caused by impairment of early left ventricular distensibility; and (3) this ratio should be determined in patients with other forms of heart disease to determine its specificity.

The relation of the qualitative and quantitative aspects of apexcardiography to the diagnosis of coronary artery disease has been widely investigated during the past 15 years.[1–9] The correlation between the height of the apexcardiographic *a* wave and direct intracardiac measurement of left ventricular end-diastolic pressure during the resting basal state has been emphasized.[3] Despite this relation, patients with coronary artery disease and elevated left ventricular filling pressure may manifest a normal-sized *a* wave in the apexcardiogram as a result of impaired left atrial contraction.[10]

Alterations in left ventricular compliance resulting from myocardial ischemia have been stressed[11–16]; increased diastolic stiffness in this setting may reduce the duration of the rapid filling wave in relation to that of the slow filling wave in the apexcardiogram. This paper describes the relative duration of rapid and slow filling periods in the apexcardiogram of subjects with documented coronary artery disease. The results obtained are compared with data from a group of patients with no evidence of heart disease on catheterization.

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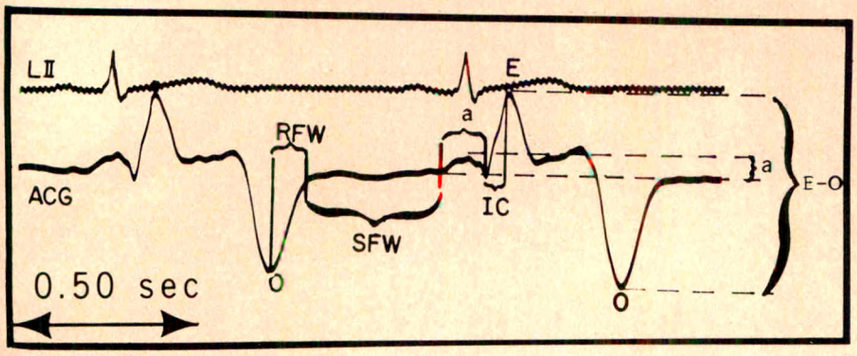

FIGURE 1. Simultaneous lead II (L II) of electrocardiogram and apexcardiogram (ACG) indicating method of measurement. The *a* wave height and the amplitude of the total apexcardiographic deflection (E-O) (H) are shown. IC = isovolumic contraction period; RFW = duration of rapid filling wave; SFW = duration of slow filling wave.

Material and Methods

Patients: The 68 patients studied were consecutive normal patients or patients with coronary artery disease and sinus rhythm who had a technically satisfactory apexcardiogram in the 24 hours before cardiac catheterization. Of 108 successive patients with suspected cardiovascular disorders who underwent apexcardiography and invasive studies, appropriate apex recordings were obtained in 99 (92 percent).

Group I consisted of 17 patients with a systolic murmur or atypical chest pain originally attributed to heart disease. There were 10 women and 7 men, aged 16 to 68 years (mean 46). Their catheterization studies were normal.

Group II consisted of 34 patients with significant coronary artery disease (greater than 75 percent obstruction) and a left ventricular end-diastolic pressure greater than 12 mm Hg. There were 28 men and 6 women, aged 36 to 76 years (mean 56). No subject in this group had coexisting hypertension or valvular heart disease.

Group III consisted of 17 patients, 12 men and 5 women aged 47 to 72 years (mean 58). All had significant coronary artery disease and a left ventricular end-diastolic pressure less than 12 mm Hg. No patient in this group had hypertension or valvular heart disease.

Apexcardiography: This procedure was performed in a vibration-free recording room using established techniques.[17] With the patient in the left lateral decubitus position, the maximal point of the apical impulse was identified, and the impulse was recorded using a hand-held Hewlett Packard APT-16 transducer connected to a 5 volt power supply and the alternating current terminal of an Electronics for Medicine amplifier. Tracings were recorded on an oscilloscopic photographic recorder at a paper speed of 75 mm/sec with 0.04 second time lines.

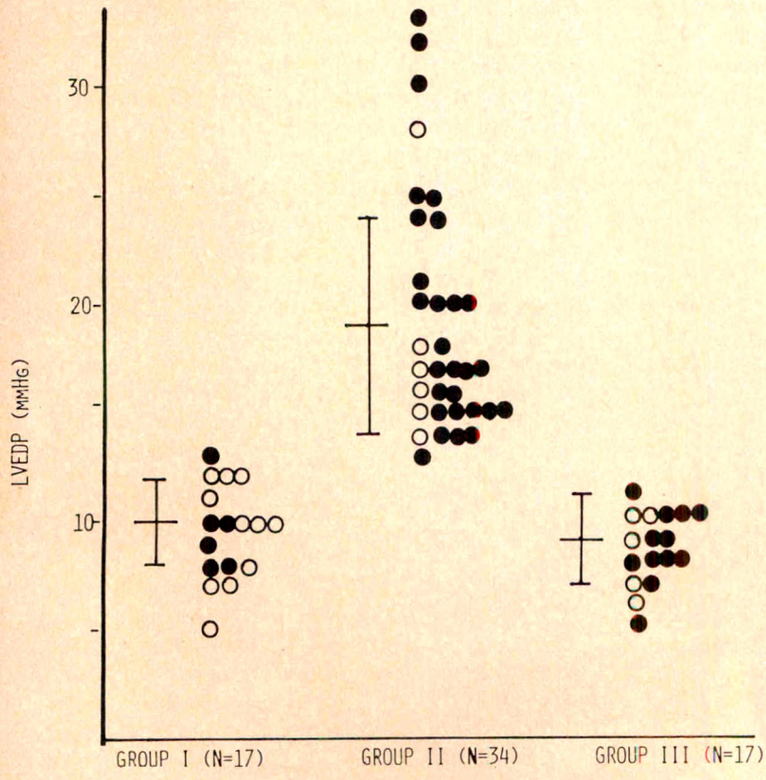

FIGURE 2. Distribution of left ventricular end-diastolic pressure (LVEDP) in the three groups. **Bars** indicate mean values ±1 standard deviation. **Closed circles** indicate male and **open circles** female patients. N = number of patients.

The apexcardiogram was analyzed using standard methods and nomenclature. The a/H ratio represented the height (in mm) of the apical *a* wave divided by the total deflection of the tracing as measured from the O point to the E point. This ratio was multiplied by a factor of 100 and expressed as a percent. The duration of the rapid filling wave (RFW) was measured (in msec) from its beginning (O point) to the site where the contour deviated toward the horizontal. The duration of the slow filling wave (SFW) was measured from the terminus of the rapid filling wave to the beginning of the *a* wave (Fig. 1).

The SFW/RFW duration ratio was then calculated for each subject. All such measurements represented the average of three successive cardiac cycles determined by two observers unaware of the clinical or catheterization data. Internal consistency was ascertained by obtaining independent measurements from both observers in a "blind" fashion, that is, so that neither physician knew the final invasively determined diagnosis. Interobserver variation was minimal, accounting for a difference in the RFW/SFW ratio greater than 5 percent in only 4 of 68 patients (5.8 percent). In these four cases, the

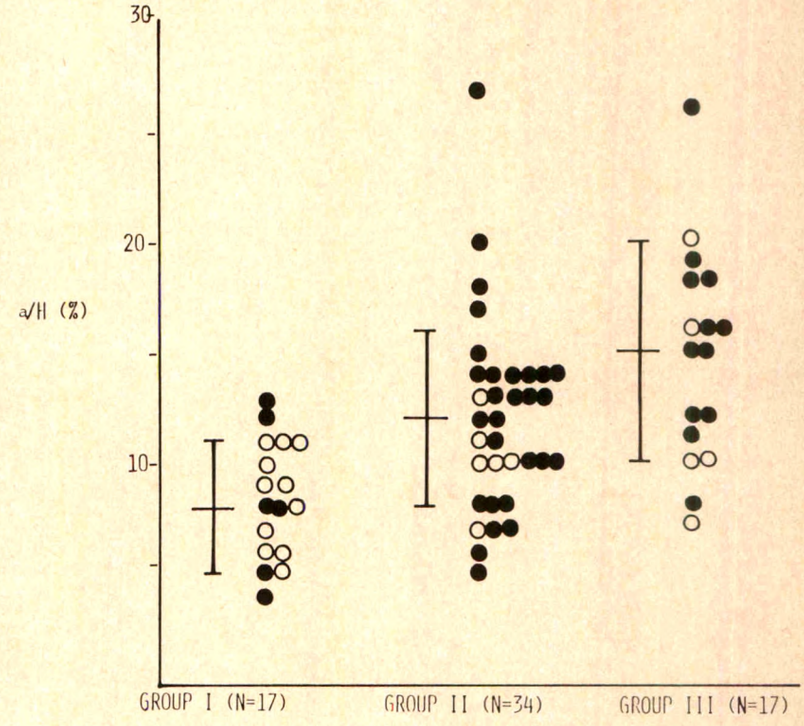

FIGURE 3. Distribution of ratios of *a* wave amplitude to total apexcardiographic deflection (a/H) in the three groups. Symbols and abbreviations as in Figure 2.

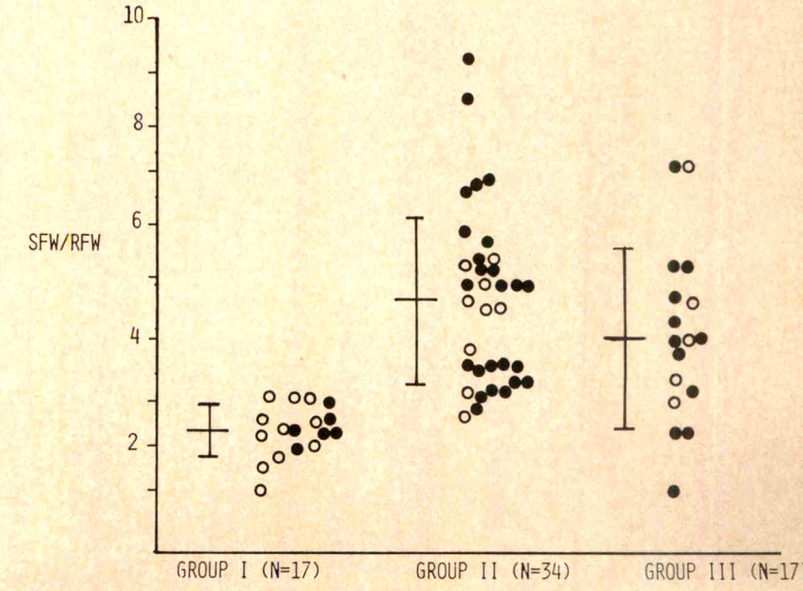

FIGURE 4. Distribution of the slow filling wave/rapid filling wave period ratio (SFW/RFW) in the three groups. Symbols and abbreviations as in Figure 2.

TABLE I

Mean Values (±1 standard deviation) for Age, a/H Ratio, Left Ventricular End-Diastolic Pressure (LVEDP), SFW/RFW Ratio, Heart Rate and Probability Values for the Three Groups

	Group I	Group II	Group III	Probability I vs. II	Probability I vs. III	Probability II vs. III
Age (yr)	46 ± 13	56 ± 11	58 ± 7	<0.002	<0.002	NS
a/H (%)	8 ± 3	12 ± 4	15 ± 5	<0.002	<0.0005	<0.02
LVEDP (mm Hg)	10 ± 2	19 ± 5	9 ± 2	<0.001	NS	<0.0005
SFW/RFW	2.3 ± 0.5	4.7 ± 1.6	4.0 ± 1.7	<0.001	<0.0005	NS
Heart rate (beats/min)	73 ± 16	71 ± 16	67 ± 9	NS	NS	NS

NS = not significant ($P > 0.05$).

apexcardiograms were jointly studied by the observers and another investigator who did not know the anatomic findings.

Cardiac catheterization: This procedure was performed with the patient supine and in the postabsorptive, nonsedated state. Left ventricular pressures were obtained with saline-filled catheters connected to a Statham strain gauge and recorded on an Electronics for Medicine DR-12 recorder. End-diastolic pressures were recorded before coronary arteriography. Coronary cineangiography was performed with 75 percent Hypaque® using the Sones or Judkins technique. Occlusive disease causing a reduction greater than 50 percent in luminal diameter was considered to represent 75 percent cross-sectional obstruction to flow. In 88 percent of subjects, nitrites, propranolol (given to 15 of 51 patients [29 percent] with angina pectoris) and other medications were withheld for 48 hours before cardiac catheterization. No patient received pharmacologic agents for at least 8 hours before catheterization and apex recording.

Probability values were obtained using Student's *t* test for unpaired measurements.

Results

Figures 2 to 4 show the values for left ventricular end-diastolic pressure, a/H ratio and slow filling to rapid filling (SFW/RFW) period ratios for patients in the three groups. Table I lists the mean (±1 standard deviation) determinations for those measurements, along with the age, the heart rate and the significance of the difference among the data in each group. The heart rates, measured at the time of noninvasive study, were not significantly different in the three study groups. When the upper limit of normal for the a/H ratio was set at 14 percent, only 10 of 34 patients (29 percent) with coronary artery disease and a left ventricular end-diastolic pressure greater than 12 mm Hg (group II) had an abnormal value. Ten of 17 subjects (59 percent) with coronary artery disease and an end-diastolic pressure less than 12 mm Hg (group III) had an a/H ratio greater than or equal to 14 percent, whereas no patient in the control group (group I) had an abnormally large *a* wave. The a/H ratio was significantly lower in the control patients than in the patients with coronary artery disease.

Patients with coronary artery disease versus normal subjects: There were no significant differences between the SFW/RFW ratios of the patients with coronary artery disease in groups II and III. When the SFW/RFW of control subjects were compared with those of patients with coronary artery disease, the differences were highly significant (group I, 2.3 ± 0.5; group II, 4.7 ± 1.6; group III, 4 ± 1.7; groups II and III versus group I, $P < 0.001$). The SFW/RFW value of 2.8 (mean + 1 standard deviation) was arbitrarily selected as a value that might prove of clinical use. A review of individual data revealed that only 2 of 17 subjects (12 percent) with no evidence of heart disease at catheterization had an SFW/RFW value greater than 2.8 compared with 32 of 34 patients (94 percent) in group II and 12 of 17 patients (71 percent) in group III. When the a/H and SFW/RFW sensitivity levels for detecting coronary artery disease (51 patients) were compared, the relative rates were: a/H greater than 14 percent, 20 of 51 patients (39 percent); SFW/RFW greater than 2.8, 44 of 51 patients (86 percent). Only 2 of 51 subjects (4 percent) with coronary artery disease had an a/H value greater than 14 percent with an SFW/RFW value of less than 2.8; both of these subjects had normal left ventricular end-diastolic pressure.

Correlation with age: The mean age of patients in group I (46 ± 13 years) was significantly lower ($P < 0.002$) than that of patients in groups II (56 ± 11 years) and III (58 ± 7 years). Therefore the SFW/RFW values were plotted against age for all 68 patients studied, revealing an insignificant degree of positive correlation ($r = 0.12$). The paired a/H and SFW/RFW ratios were also plotted against age, disclosing a significant ($P < 0.005$) but relatively low degree of positive correlation ($r = 0.34$). The correlation coefficient for left ventricular end-diastolic pressure and SFW/RFW ratio in group II was 0.19.

Discussion

The influence of myocardial ischemia on the diastolic configuration of the apexcardiogram has been intensively investigated. Both spontaneous and exercise-induced episodes of angina pectoris can produce an increase in the height of the *a* wave and in some cases a prominent rapid filling wave.[4,5,17] These events frequently correlate with the appearance of the fourth and third heart sounds, respectively. Such dynamic changes have been ascribed to diminished distensibility of the left ventricular myocardium during periods of oxygen deprivation.[18]

Attenuation of early left ventricular filling related to diminished compliance: This study was prompted by the suggestion that early filling of the left ventricle might be attenuated in patients with coronary

artery disease. Indeed, sequential diastolic volume measurements in subjects with sinus rhythm indicate that the amount of filling in the first third of diastole is 38 percent in normal subjects but only 25 percent in patients with coronary artery disease and abnormal segmental left ventricular contraction.[11] We surmise that an abbreviation of the rapid filling period (RFW) in relation to the slow filling period (SFW) in the basal setting of significant coronary artery disease is a correlate of diminished left ventricular compliance. The increased SFW/RFW ratio in our patients with coronary artery disease was not a result of alterations in heart rate or left ventricular end-diastolic pressure because there was no significant difference among cardiac cycle lengths in the three groups and no major correlation between the SFW/RFW ratio and end-diastolic pressure in group II ($r = 0.19$). Although the mean age of patients in the control group was less than that of patients in groups II and III, there was no significant correlation between age and the SFW/RFW ratio.

Limitations of such study: The apexcardiogram and measurement of left ventricular end-diastolic pressure were not simultaneously performed in any patient studied. The mean a/H ratio was significantly higher (15 ± 5 versus 12 ± 4 percent; $P < 0.02$) in patients in group III, who had an end-diastolic pressure of 9 ± 2 mm Hg, than in patients in group II, who had a higher mean pressure (19 ± 5 mm Hg). This difference may be due to variations in the responses of patients in the two groups to undergoing cardiac catheterization without sedation. Much published data[7] indicate that an abnormal a/H ratio is useful for identifying elevated end-diastolic pressure when both are assessed together. In addition, both measurements frequently increase during an acute episode of angina. However, we believe that during the past 5 years cardiac catheterization has been performed in more patients with angina pectoris, coronary atherosclerosis and normal basal left ventricular end-diastolic pressure than in the past, possibly because of improved techniques for myocardial revascularization. A larger number of such patients with labile left ventricular end-diastolic pressure would reduce the value of the resting a/H ratio as measured with the apexcardiogram. The possible "diluting" effect of this patient group on the traditional noninvasive markers of left ventricular dysfunction is being studied.

A curtailment of early left ventricular filling in patients with coronary disease is indirectly suggested by our data. Volume-pressure loops were not constructed, and sequential angiographic studies of left ventricular filling were not performed to evaluate myocardial compliance or changes in volume during various phases of diastole. Such studies may provide insight into the enhanced SFW/RFW relation in patients with myocardial ischemia.

In this study the SFW/RFW ratio was measured in patients with isolated coronary artery disease and compared with the ratio in patients with no evidence of heart disease on catheterization. The influence of other cardiovascular diseases on the SFW/RFW ratio is unknown and warrants further investigation. It should be stressed that our control group consisted of 17 subjects with a systolic murmur or atypical chest pain originally attributed to heart disease. The majority of such patients were women with a mean age 10 years less than that of the patients with coronary disease. The *ideal* control group would consist of age- and sex-matched subjects without symptoms or signs of a cardiovascular disorder. The ethical or medicolegal constraints implicit in performing cardiac catheterization in such subjects are clear. However, results of the isolated noninvasive study of asymptomatic persons with a normal physical examination must be viewed with caution because the prevalence of subclinical coronary artery disease in the 56 year old predominantly male group is unknown.[19] A definition of "normal" for patients who have undergone cardiac catheterization has not been established.

Advantages of the study: Apexcardiography is a simple noninvasive technique that is readily available and easy to use in studying patients with suspected coronary artery disease. Our data suggest that the ratio of slow filling period to rapid filling period (SFW/RFW) determination frequently (in 86 percent of our patients) exceeds 2.8 in patients with angiographically demonstrable occlusive coronary artery disease and identifies 94 percent of patients with a left ventricular end-diastolic pressure greater than 12 mm Hg. This externally derived measurement appears more sensitive than the a/H ratio for ascertaining the presence or absence of coronary atherosclerosis in patients with a chest pain syndrome. A few patients with coronary artery disease had an a/H ratio greater than 14 percent and an SFW/RFW ratio less than 2.8, indicating that the diagnostic accuracy of the apexcardiogram is enhanced when both measurements are considered. The method also provides a useful adjunct to the treadmill stress test, which results in S-T segment and U wave abnormalities in 88 percent of patients with exertional angina and a normal resting electrocardiogram when chest pain is reproduced during exercise.[20]

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References

1. **Benchimol A, Dimond EG:** The normal and abnormal apexcardiogram. Its physiologic variation and its relation to intracardiac events. Am J Cardiol 12:368–382, 1963
2. **Coulshed N, Epstein EJ:** The apex cardiogram: its normal features explained by those found in heart disease. Br Heart J 25:697–708, 1963
3. **Voigt GC, Friesinger GC:** The use of apexcardiography in the assessment of left ventricular diastolic pressure. Circulation 41: 1015–1024, 1970
4. **Benchimol A, Dimond EG:** The apex cardiogram in ischaemic heart disease. Br Heart J 24:581–594, 1962
5. **Benchimol A, Dimond EG:** The apexcardiogram in normal older

subjects and in patients with arteriosclerotic heart disease. Effect of exercise on the "a" wave. Am Heart J 65:789–801, 1963
6. **Ginn WM, Sherwin RW, Harrison WK, et al:** Apexcardiography: use in coronary heart disease and reproducibility. Am Heart J 73:168–180, 1967
7. **McGinn FX, Gould L, Lyon AF:** The phonocardiogram and apexcardiogram in patients with ventricular aneurysm. Am J Cardiol 21:467–477, 1968
8. **El-Sherif, Saad Y, El-Said G:** Praecordial tracings of myocardial aneurysms. Br Heart J 31:357–364, 1969
9. **Harrison TR, Hughes L:** Precordial systolic bulges during anginal attacks. Trans Assoc Am Phys 71:174–185, 1958
10. **Braunwald E, Frahm CJ:** Studies on Starling's law of the heart. IV. Observations on the hemodynamic functions of the left atrium in man. Circulation 24:633–642, 1961
11. **Miller RR, Zelis R, Massumi RA, et al:** Left ventricular compliance: relation to different patterns of left ventricular dyssynergy (abstr). Am J Cardiol 31:147, 1973
12. **Forrester JS, Diamond G, Parmley WW:** Early increase in left ventricular compliance after myocardial infarction. J Clin Invest 51:598–603, 1972
13. **Dodek A, Kassebaum DG, Bristowe JD:** Pulmonary edema in coronary-artery disease without cardiomegaly: paradox of the stiff heart. N Engl J Med 286:1347–1350, 1972
14. **Covell JW, Ross J Jr:** Nature and significance of alterations in myocardial compliance. Am J Cardiol 32:449–455, 1973
15. **Levine HJ:** Compliance of the left ventricle. Circulation 46: 423–426, 1972
16. **Miller RR, DeMaria AN, Amsterdam EA, et al:** Improvement of reduced left ventricular diastolic compliance in ischemic heart disease after successful coronary artery bypass surgery. Am J Cardiol 35:11–16, 1975
17. **Benchimol A:** Noninvasive Diagnostic Techniques in Cardiology. Baltimore, Williams & Wilkins, 1977, p 11–12
18. **Muller O, Rorvik K:** Haemodynamic consequences of coronary heart disease with observations during anginal pain and on the effect of nitroglycerin. Br Heart J 20:302–310, 1958
19. **Erikssen J, Enge I, Forfang K, et al:** False positive diagnostic tests and coronary angiographic findings in 105 presumably healthy males. Circulation 54:371–376, 1976
20. **Faris JV, McHenry PL, Morris SN:** Concepts and applications of treadmill exercise testing and the exercise electrocardiogram. Am Heart J 95:102–114, 1978

Mitral Valve Motion and Changes in Left Ventricular End-Diastolic Pressure: A Correlative Study Of the PR-AC Interval

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To evaluate the relation between mitral valve motion and left ventricular end-diastolic pressure, the PR-AC interval, an index derived from the electrocardiogram and mitral echogram, and the left ventricular end-diastolic pressure were determined simultaneously in 22 patients undergoing diagnostic cardiac catheterization. Intravenous infusion of dextran or administration of nitroglycerin was used to alter left ventricular end-diastolic pressure to determine if there was a predictive relation between this pressure and the PR-AC interval during acute hemodynamic manipulations. There was a weak negative correlation ($r = -0.33$, $P < 0.01$) between this pressure and the PR-AC interval. At rest a PR-AC interval greater than 0.06 second correctly predicted a left ventricular end-diastolic pressure of less than 20 mm Hg in 15 of 16 subjects. However, in four of six subjects with a PR-AC interval of 0.06 second or less, the end-diastolic pressure was less than 20 mm Hg. After interventions that varied left ventricular end-diastolic pressure by a factor of 2, the PR-AC interval changed slightly or not at all. These data suggest that the PR-AC interval is of limited value in predicting abnormal values or serial changes in left ventricular end-diastolic pressure.

There is currently great interest in the use of echocardiography to assess left ventricular function. Echocardiographic indexes based on quantitation of left ventricular diameter and its changes during the cardiac cycle have been validated as useful measures of left ventricular performance.[1]

Because left ventricular end-diastolic pressure increases with decreased left ventricular compliance or pump failure, a noninvasive technique that could reliably predict this pressure would be of great value. Konecke et al.[2] reported that a PR-AC interval of 0.06 second or less, a value derived from the electrocardiogram and mitral valve echogram, can predict elevation of left ventricular end-diastolic pressure to values of 20 mm Hg or greater, provided that the atrial component of the left ventricular pressure pulse is at least 8 mm Hg.[2] They also found that a PR-AC interval greater than 0.06 second was associated with a left ventricular end-diastolic pressure of less than 20 mm Hg in most cases, the three exceptions occurring when an end-diastolic pressure of more than 20 mm Hg occurred with an *A* wave of less than 8 mm Hg. The PR-AC interval has also been reported to have prognostic value in patients with acute transmural myocardial infarction and in predicting surgical mortality in patients undergoing left ventricular aneurysmectomy or coronary bypass surgery.[3–5] However, the studies on which these data are based were all performed with subjects in the resting state. In this study we therefore manipulated left ventricular end-diastolic pressure in a group of patients while recording the mitral valve echogram to determine if the PR-AC interval would prove useful in monitoring

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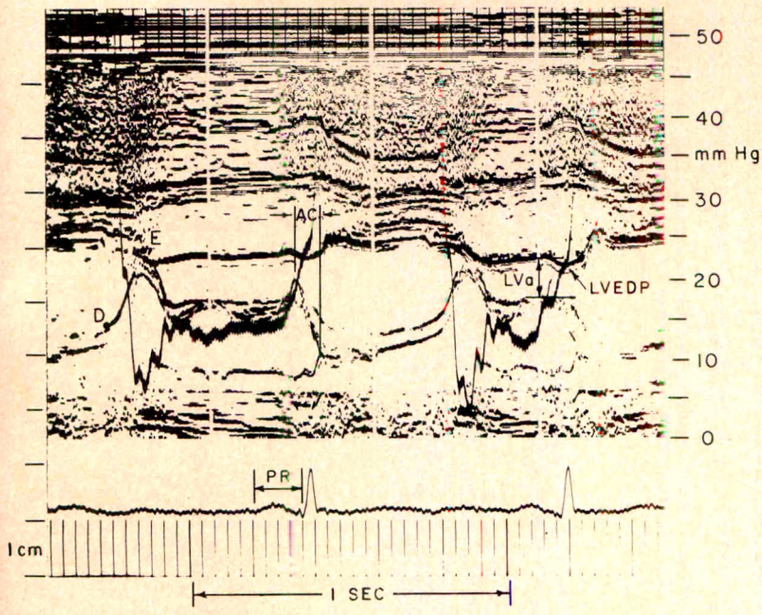

FIGURE 1. Simultaneous mitral valve echogram, electrocardiogram and left ventricular pressure on a high sensitivity scale to illustrate the method of determining PR-AC interval and the size of the left ventricular *A* wave. Vertical lines are drawn at the time of the mitral valve A point (onset of mitral valve closure) and C point (closure of mitral valve where both leaflets come into apposition). The difference (in seconds) between the A-C interval (AC) derived from the mitral valve echogram and the P-R interval (PR) derived from the electrocardiogram gives the PR-AC interval. LVa = left ventricular pressure *A* wave indicated by **vertical arrows;** LVEDP = left ventricular end-diastolic pressure.

changes in left ventricular end-diastolic pressure due to various interventions.

Methods

Patients: Twenty-two patients undergoing diagnostic cardiac catheterization were studied after giving informed consent. There were 15 men and 7 women with a mean age of 49 years (range 36 to 62). The postcatheterization diagnoses included coronary artery disease (9 patients), pulmonary stenosis (1 patient) and chest pain with a normal coronary arteriogram (12 patients). All patients had sinus rhythm.

Procedures: *Echocardiograms* were obtained in the M mode at a paper speed of 100 mm/sec using a Smith-Kline Instruments ultrasonoscope interfaced with a Cambridge fiberoptics multichannel recorder. Left heart pressure was obtained with a fluid-filled catheter connected to a Statham P23Db strain gauge with zero set at a level 5 cm below the angle of Louis with the patient supine.

After right and left heart catheterization, a control mitral echogram, lead II of the electrocardiogram and left ventricular pressure were recorded simultaneously on the same strip chart recorder. In four patients with a resting left ventricular end-diastolic pressure of 20 mm Hg or greater, nitroglycerin, 0.3 mg sublingually, was given to reduce the pressure and the mitral echogram, electrocardiogram and left ventricular pressure were recorded 2, 5, 10 and 15 minutes later. In the 18 patients with a resting left ventricular end-diastolic pressure of less than 20 mm Hg, low molecular weight dextran (Rheomacrodex®) was infused intravenously at 30 ml/min, and the same recordings were made after each 100 ml increment until the end-diastolic pressure reached 25 mm Hg or 500 cc of dextran had been given. In three patients, the legs were elevated at the end of infusion to increase further end-diastolic pressure. In one patient, the mitral valve echogram and left ventricular pressure were recorded after a left ventriculogram, and then nitroglycerin was administered to reduce left ventricular filling pressure. In the remaining subjects, angiography was performed after the hemodynamic studies.

The PR-AC interval: This interval was derived from the electrocardiogram and mitral valve echocardiogram using the technique described by Konecke et al.[2] (Fig. 1). The P-R interval, defined as the interval from the onset of the P wave to the beginning of the QRS complex, was measured in seconds from lead II of the electrocardiogram. Both mitral leaflets were visualized in the echocardiogram of 20 subjects; in 2 patients only the anterior leaflet was seen. The A-C interval, measured in seconds, was defined as the time interval between the A point of the mitral echogram to mitral closure (C point), indicated by the apposition of the mitral leaflets or the termination of anterior leaflet closing motion when the posterior leaflet was not visualized. These two measurements were averaged over at least five consecutive cardiac cycles, and the PR-AC interval was then calculated as the difference between the P-R and A-C intervals. Left ventricular pressure was recorded at a high sensitivity level (Fig. 1), and left ventricular end-diastolic pressure, defined as the nadir or inflexion after the *A* wave, was averaged over the same five consecutive cycles from which the PR-AC interval was derived. The magnitude of the left ventricular pressure *A* wave, measured from its onset after the P wave of the electrocardiogram to its peak, was also averaged over five cardiac cycles.

Results

Relation between PR-AC interval and left ventricular end-diastolic pressure at rest: This relation in the 22 subjects is illustrated graphically in Figure 2. Of the 16 patients who had a PR-AC interval greater than 0.06 second, only 1 had a left ventricular end-diastolic pressure greater than 20 mm Hg and an *A* wave of 8 mm Hg. Therefore in the resting state a PR-AC interval greater than 0.06 second correctly predicted an end-diastolic pressure of less than 20 mm Hg in 15 of 16 subjects (94 percent). However, of the six patients with a PR-AC interval of 0.06 second or less, only two had an end-diastolic pressure of 20 mm Hg or more. Thus, the data in five patients did not fall into the pattern predicted by the previously reported relation between the PR-AC interval and left ventricular end-diastolic pressure at rest.[2]

Effects of dextran and nitroglycerin administration: The relation between the PR-AC interval and left ventricular end-diastolic pressure is plotted in Figure 3 for both the resting values and those obtained after administration of dextran or nitroglycerin. A total of 112 paired values of left ventricular end-diastolic pressure and PR-AC interval were available for analysis. A wide scatter of the points relating these two variables is evident, and the correlation coefficient was low ($r = -0.33$) although statistically significant ($P < 0.01$). When only subjects with a left ventricular end-diastolic pressure of 20 mm Hg or more and a left ventricular *A* wave of 8 mm Hg or more were considered (17 paired values), the PR-AC interval varied from 0.03 to 0.08 second.

In seven of these pairs the PR-AC interval was more than 0.06 second, whereas in 10 it was less. There were 13 paired values with a PR-AC greater than 0.06 second in which the left ventricular end-diastolic pressure was 20 mm Hg or more, and in 7 of them the *A* wave was 8 mm Hg or more. On the other hand, in 28 of the 46 paired values in which end-diastolic pressure was less than 20 mm Hg, the PR-AC interval was 0.06 second or less. Thus, considering the resting values and postintervention results, there was no PR-AC value that could reliably separate the normal from elevated levels of left ventricular end-diastolic pressure.

Variability in directional changes: In the 18 patients receiving dextran infusion, the left ventricular end-diastolic pressure increased from 11 ± 4 mm Hg (mean ± standard deviation) to 23 ± 3 mm Hg, whereas the PR-AC interval decreased from 0.08 ± 0.02 second to 0.06 ± 0.01 second. Thus, the directional changes were consistent with the previously reported inverse relation between left ventricular end-diastolic pressure and the PR-AC interval. However, the individual data reveal marked variation in this relation. For example, Patient 1 (Fig. 4) had at rest a normal left ventricular end-diastolic pressure of 12 mm Hg and a PR-AC interval of 0.09 second. When end-diastolic pressure in-

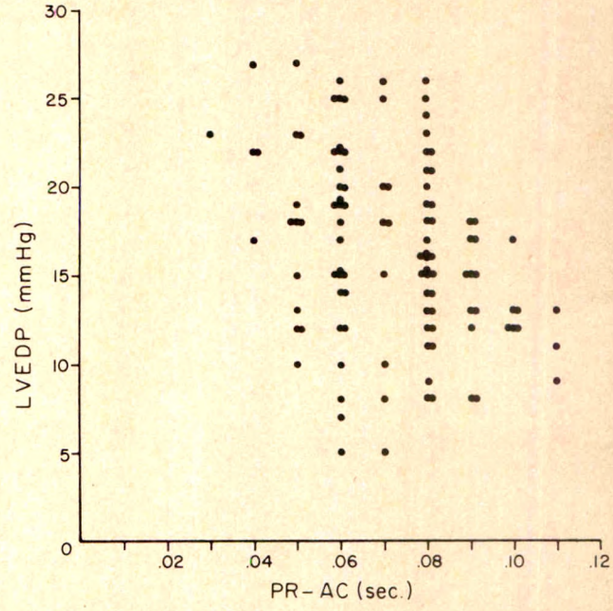

FIGURE 3. Relation between the PR-AC interval and left ventricular end-diastolic pressure (LVEDP) including resting data and points after interventions (dextran infusion or nitroglycerin administration) to vary the end-diastolic pressure. $r = -0.33$; $P < 0.01$.

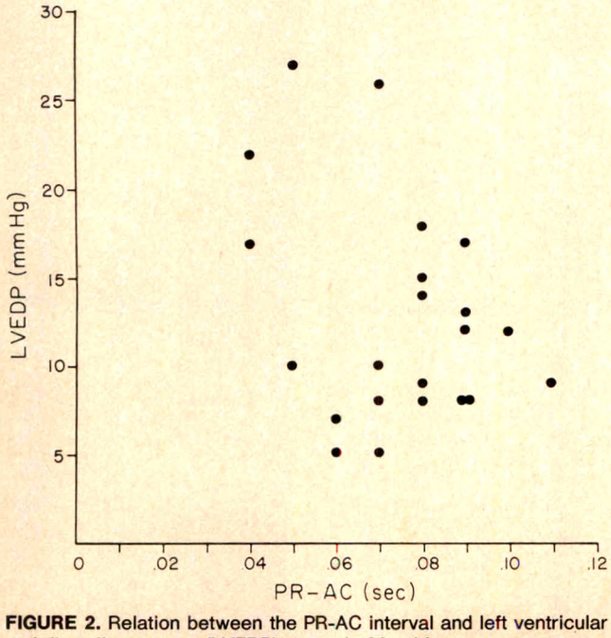

FIGURE 2. Relation between the PR-AC interval and left ventricular end-diastolic pressure (LVEDP) at rest in 22 subjects.

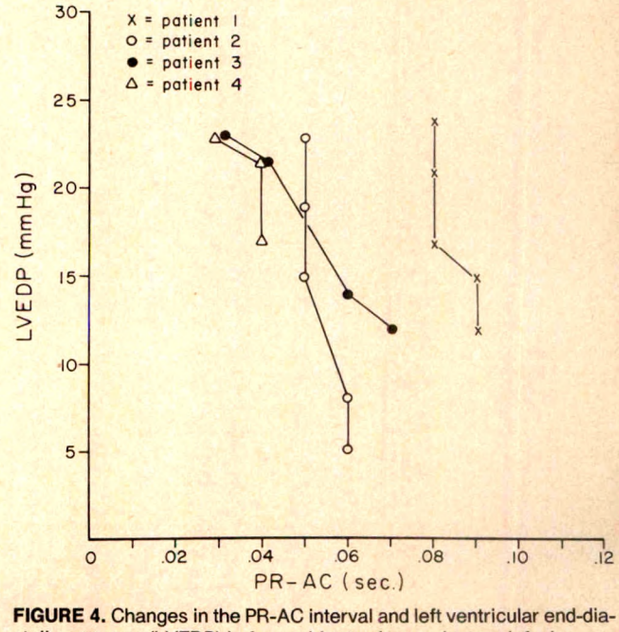

FIGURE 4. Changes in the PR-AC interval and left ventricular end-diastolic pressure (LVEDP) in four subjects given a dextran infusion.

creased twofold to 24 mm Hg with dextran infusion, the PR-AC interval decreased only slightly to 0.08 second. With dextran infusion Patient 2 showed a decrease in the PR-AC interval from 0.06 to 0.05 second which, according to Konecke et al.,[2] should have predicted a high end-diastolic pressure, but in fact this pressure was only 15 mm Hg. There was no further change in the PR-AC interval as the end-diastolic pressure increased to 23 mm Hg. In Patient 3 there was a clear inverse relation between the two variables: As the PR-AC interval decreased from 0.08 to 0.03 second after dextran infusion, the end-diastolic pressure increased from 12 to 23 mm Hg. Patient 4 had a low PR-AC interval (0.04 second) at rest with an end-diastolic pressure of 17 mm Hg; with infusion, the PR-AC interval decreased minimally to 0.03 second, whereas the end-diastolic pressure increased to 23 mm Hg. In all four subjects the PR-AC interval decreased as left ventricular end-diastolic pressure increased, but in three of the four the decrease was very slight (0.01 second). The majority of the remaining subjects also showed only a slight or no change in the PR-AC interval with infusion.

Discussion

The PR-AC interval as a predictor of left ventricular diastolic pressure: Konecke et al.[2] described an inverse relation between left ventricular end-diastolic pressure and the PR-AC interval. They suggested that the A-C interval lengthens when left ventricular compliance decreases for the following reasons: The more rapid than usual increase in atrial pressure followed by an immediate increase in left ventricular pressure results in early crossover of these pressures, and hence the onset of mitral closure (A point) occurs early; complete closure of the mitral valve (C point) occurs at a higher left ventricular pressure and is thus delayed; the net effect of these two changes would be a lengthening of the A-C interval. Because the duration of atrioventricular conduction also influences the onset of mitral closure, Konecke et al. chose to allow for this factor by measuring the difference between the PR and AC intervals. Expressing their findings in more quantitative terms they reported that a PR-AC interval of 0.06 second or less was associated with a left ventricular end-diastolic pressure of 20 mm Hg or more and an *A* wave of 8 mm Hg or more in each of their cases. They also found that when the PR-AC interval was greater than 0.06 second, the left ventricular end-diastolic pressure was less than 20 mm Hg or was 20 mm Hg or more with an *A* wave of less than 8 mm Hg.

In the 22 patients we studied at rest, our data revealed five exceptions to their predictions; in four of these left ventricular end-diastolic pressure was overestimated. In 94 percent of the resting subjects, a PR-AC value greater than 0.06 second correctly predicted a left ventricular end-diastolic pressure of less than 20 mm Hg. A low PR-AC value (0.06 second or less) was less reliable because it had a 66 percent false positive rate in predicting an end-diastolic pressure of 20 mm Hg or more. Differences were more striking when we studied the relation between the PR-AC interval and left ventricular end-diastolic pressure after interventions that modified the end-diastolic pressure. In contrast to the findings at rest, only slightly more than half (28 of 46) of PR-AC values of 0.06 second or less were associated with a left ventricular end-diastolic pressure of less than 20 mm Hg. In addition, in 13 instances a PR-AC interval greater than 0.06 second was associated with an end-diastolic pressure of 20 mm Hg or more, and in 7 of these the *A* wave was 8 mm Hg or more. Although there was a weak negative correlation between the PR-AC interval and left ventricular end-diastolic pressure ($r = -0.33$) after the drug interventions, because of the wide scatter of data there was no PR-AC value that could separate normal from elevated levels of left ventricular end-diastolic pressure. Thus, the PR-AC interval did not dependably predict normal or elevated left ventricular end-diastolic pressure after an intervention, although an interval greater than 0.06 second at rest usually was a reliable predictor of a left ventricular end-diastolic pressure of less than 20 mm Hg.

PR-AC relation over a wide range of left ventricular end-diastolic pressure: We found that in a given subject the PR-AC interval may remain constant or show only minor change over a wide range of left ventricular end-diastolic pressures when these pressures are raised or lowered by administration of nitroglycerin or dextran. Thus, the PR-AC interval would be of little use in serial studies of left ventricular end-diastolic pressure after a therapeutic intervention or when looking for evidence of deterioration of ventricular function. In a similar study Yow et al.[6] also were unable to demonstrate any simple quantitative relation between the PR-AC interval and left ventricular end-diastolic pressure when the latter was varied from 1 to 28 mm Hg with interventions such as nitroglycerin administration, atrial pacing or angiography.

Factors influencing mitral valve closure and the P-R interval: Corya et al.[3] recently reported that in a group of 204 patients with coronary artery disease, a PR-AC interval of 0.06 second or less was associated with a resting left ventricular end-diastolic pressure ranging from 3 to 34 mm Hg (mean 11) in those with normal left ventricular dimensions and 5 to 28 mm Hg (mean 23) in those with an increase in left ventricular diameter. Thus, factors other than the left ventricular end-diastolic pressure apparently influence mitral valve closure. Feigenbaum[7] also noted some exceptions to the previously predicted relation between the PR-AC interval and left ventricular end-diastolic pressure. He suggested that some of these discrepancies may occur in subjects with a very short P-R interval (less than 0.14 second), which would have the effect of decreasing the PR-AC interval. Interestingly, two of the four subjects in Figure 2 who had an inappropriately low PR-AC interval at rest in the presence of a normal left ventricular end-diastolic pressure had a P-R interval of less than 0.14 second. Of the 28 PR-AC values in Figure 3 that were inappropriately low when associated with a left ventricular end-diastolic pressure of less than 20 mm Hg, only 6 were associated with a P-R interval of less than 0.14 second. Thus, most of the exceptions to the

predicted relation between the PR-AC interval and left ventricular end-diastolic pressure could not be explained on the basis of a P-R interval of less than 0.14 second.

Clinical implications: This study has examined the previously reported quantitative relation between the PR-AC interval, derived from the electrocardiogram and mitral valve echogram, and left ventricular end-diastolic pressure. In the resting state a PR-AC interval greater than 0.06 second correctly predicted a left ventricular end-diastolic pressure of less than 20 mm Hg in 15 of 16 subjects. A short PR-AC interval (0.06 second or less) incorrectly predicted a left ventricular end-diastolic pressure greater than 20 mm Hg in four of six subjects. A poor correlation was found between the PR-AC interval and left ventricular end-diastolic pressure after maneuvers that increased or decreased the left ventricular end-diastolic pressure. These results indicate that this noninvasive index is not reliable for predicting abnormal resting left ventricular end-diastolic pressure or for monitoring this pressure after acute interventions.

References

1. **Popp RL:** Current concepts in cardiology: Echocardiographic evaluation of left ventricular function. N Engl J Med 296:856–858, 1977
2. **Konecke LL, Feigenbaum H, Chang S, et al:** Abnormal mitral valve motion in patients with elevated left ventricular end-diastolic pressure. Circulation 47:989–996, 1973
3. **Corya BC, Rasmussen S, Knoebel SB, et al:** Echocardiography in acute myocardial infarction. Am J Cardiol 36:1–10, 1975
4. **Dillon JC, Feigenbaum H, Weyman AE, et al:** M-mode echocardiography in the evaluation of patients for aneurysmectomy. Circulation 53:657–662, 1975
5. **Corya BC, Rasmussen S, Knoebel SB, et al:** M-mode echocardiography in evaluating left ventricular function and surgical risk in patients with coronary artery disease. Chest 72:181–185, 1977
6. **Yow MV, Reichek N:** Left ventricular end-diastolic pressure and echocardiographic mitral valve closure (abstr). Circulation 52: Suppl II:II–51, 1975
7. **Feigenbaum H:** Echocardiography, second edition. Philadelphia, Lea & Febiger, 1976, p 103

Echocardiography: Pericardial Thickening and Constrictive Pericarditis

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A total of 167 patients with pericardial thickening noted on M mode echocardiography were studied retrospectively. After the echocardiogram, 72 patients underwent cardiac surgery, cardiac catheterization or autopsy for various heart diseases; 96 patients had none of these procedures. In 49 patients the pericardium was directly visualized at surgery or autopsy; 76 percent of these had pericardial thickening or adhesions. In another 8 percent, pericardial adhesions were absent, but no comment had been made about the appearance of the pericardium itself. In the remaining 16 percent, no comment had been made about the pericardium or pericardial space. Cardiac catheterization in 64 patients revealed 24 with hemodynamic findings of constrictive pericarditis or effusive constrictive disease.

Seven echocardiographic patterns consistent with pericardial adhesions or pericardial thickening are described and related when possible to the subsequent findings at heart surgery or autopsy. The clinical diagnoses of 167 patients with pericardial thickening are presented. The hemodynamic diagnosis of constrictive pericardial disease was associated with the echocardiographic finding of pericardial thickening, but there were no consistent echocardiographic patterns of pericardial thickening diagnostic of constriction. However, certain other echocardiographic abnormalities of left ventricular posterior wall motion and interventricular septal motion and a high E-F_O slope were suggestive of constriction.

The M mode echocardiographic appearance of pericardial effusion has been well characterized,[1,2] but in clinical practice one often encounters patterns that are not classic for simple effusion and that may represent pericardial thickening. Feigenbaum[2] described several echocardiographic patterns consistent with a thickened pericardium, but we are not aware of any large scale study addressing this problem. Various echocardiographic features have been reported useful in the diagnosis of constrictive pericarditis: Rapid posterior movement of the left ventricular posterior wall in early diastole, followed by a flat mid to late diastolic motion has been described.[2] Gibson et al.[3] noted abnormal interventricular septal motion characterized by a rapid anterior displacement of the left ventricular septal echo at the time of the electrocardiographic QRS complex, followed by a rapid exaggerated posterior motion in early diastole. The E-F_O slope of the anterior mitral valve leaflet was reported to be abnormally rapid in some patients with constrictive pericarditis.[2] However, no pathognomonic echocardiographic evidence for constrictive pericarditis has been found.

This study was undertaken (1) to define the significance of pericardial thickening as noted on M mode echocardiography and thus to refine further our criteria for this interpretation, (2) to investigate whether there are any patterns that are diagnostic of pericardial constriction, and (3) to investigate the incidence of pericardial constriction in patients with pericardial thickening noted in the M mode echocardiogram.

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Methods

Patient selection: All patients in this study had a diagnosis of pericardial thickening on the basis of M mode echocardiography performed at Stanford University Hospital between 1972 and 1977. Pericardial thickening was diagnosed when parallel posterior pericardial echo interfaces were noted; no specific echocardiographic system existed for differentiating types of pericardial thickening. Patients were identified from the computerized patient data base comprising all patients seen by our Cardiology Division.[4] Of the 173 patients listed, 6 were excluded because their echocardiograms were not available for review. The medical records of the remaining 167 patients were examined for the clinical diagnosis at the time of the echocardiographic examination and results of hemodynamic studies, subsequent heart surgery or autopsy.

The same computerized patient data base was used to identify all patients indexed as having a final diagnosis of constrictive pericarditis or effusive constrictive disease (24 patients) who also had an echocardiogram. The medical records and echocardiograms of these patients were then reviewed for hemodynamic, surgical and echocardiographic findings.

Echocardiographic measurements: One of us (I.S.) examined the echocardiogram of each patient for the appearance of pericardium without knowledge about the patient or his final diagnosis. When precise categorization of the pericardial elements was difficult, a second observer (R.P.) examined and categorized the appearance of the pericardium.

The left ventricular posterior wall motion, interventricular septal motion, E-F_O slope, atrial emptying index and percent fractional shortening were examined in the subgroup of patients who had cardiac catheterization (64 patients).[5] The posterior left ventricular wall was categorized as "flat" if there was an early rapid diastolic movement of the posterior left ventricular wall and no further posterior motion during the rest of diastole.[2] No attempt was made to interpret the left ventricular posterior wall motion in the presence of a large pericardial effusion (more than 500 cc).

The interventricular septal motion was examined with particular attention to the abnormalities described by Gibson et al.[3] A rapid anterior displacement of the left ventricular septum at the time of the QRS complex of the electrocardiogram, followed by a flat or slightly posterior systolic motion and a rapid exaggerated early diastolic posterior motion, is suggestive of constrictive pericarditis.[3] No attempt was made to interpret the interventricular septal motion in the presence of a large pericardial effusion.

The E-F_O slope of the mitral valve, which reflects left ventricular filling rate, was evaluated in those patients who did not have mitral stenosis, a mitral prosthetic valve or a large pericardial effusion. The range of normal values in our laboratory is 2.5 to 11.7 cm/sec.[6]

The atrial emptying index described by Strunk et al.[5] was examined in the patients whose heart rate was lower than 85 beats/min and in those who did not have mitral stenosis or a prosthetic mitral or aortic valve.

The quantification of pericardial effusion was made using the method of Horowitz et al.[1]

The percent fractional shortening of the left ventricular cavity was calculated as (Change in Left Ventricular Dimension/End-Diastolic Left Ventricular Dimension) × 100. In our laboratory normal values for this index are 28 to 41 percent.

The criterion used for the hemodynamic diagnosis of pericardial constriction was diastolic equalization (within 6 mm Hg) of pressures from the right and left ventricle and pulmonary artery, mean pulmonary wedge pressure and right atrial pressure. In patients with right heart catheterization only, pericardial constriction was assessed without measurement of the left ventricular diastolic pressure. If a pericardial effusion of more than 100 cc was noted in association with hemodynamic evidence of pericardial constriction, a diagnosis of effusive constrictive disease was made.[7]

Echocardiographic procedures: A Smith-Kline Ekoline 20A ultrasonoscope with a pulse repetition rate of 1,000/sec and an acoustically focused, standard 2.25 megahertz, 13 mm transducer was used for all cases; the resulting tracings were printed on Ekoline 21, Honeywell 1856, Irex 101 or Electronics for Medicine DR-8 recorders. Standard procedure in our laboratory requires placement of the transducer at the left sternal border in the intercostal space that permits recording of both mitral valve leaflets when the transducer is perpendicular to the chest wall. The transducer is then tilted inferolaterally to record the left ventricular cavity at the level of the chordae tendineae. While repeated cardiac cycles are recorded from this area, the damping control is altered sequentially, placing variable resistances into the pulsing circuit and producing sound pulses of variable length. Because short pulses increase the physical axial resolution of the sound and contain less absolute energy than long pulses, only the stronger reflecting interfaces are recorded with maximal damping (short pulse).[8] The gain settings permitting optimal visualization of the weak endocardial echoes are used with minimal damping (long pulse) as a basis for subsequent damping steps. Maximal damping permits optimal identification of individual echoes in the area of the posterior pericardium and gives an indication of the relative echo intensity of the recorded echoes. In each case, multiple damping settings are used. Since 1975 a switched gain circuit has been present in our instruments. This circuit reduces the amplifier gain to a preset level 100 times/sec, thereby highlighting the strong echoes in the vicinity of the posterior pericardium.

All patients were studied in the 30° left lateral decubitus position with the head and thorax slightly elevated.

Results

Of the 167 patients identified as having pericardial thickening on M mode echocardiography, 71 patients

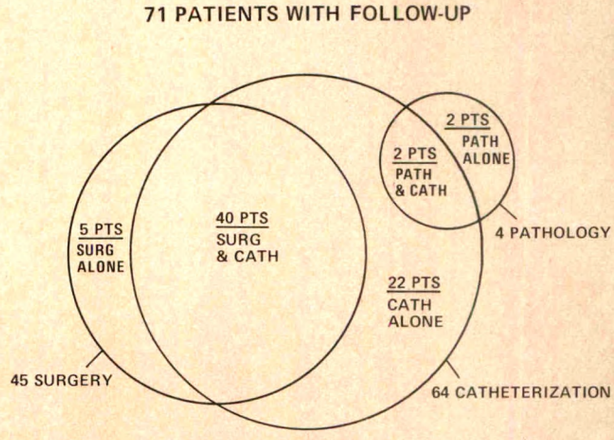

FIGURE 1. Diagram of 71 patients (PTS) undergoing surgery (SURG), cardiac catheterization (CATH) and autopsy (PATH) after echocardiography.

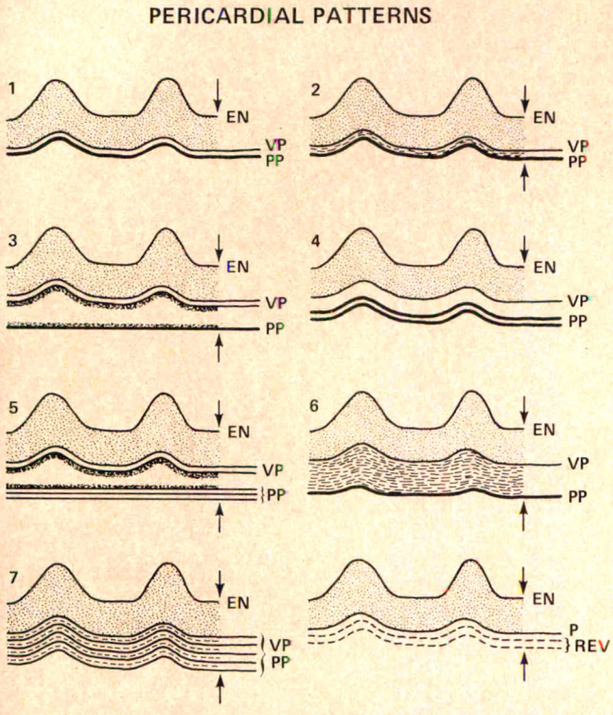

FIGURE 2. Diagrammatic representation of patterns of pericardial thickening used in this study. Patterns 1 through 7 are suggestive of pericardial thickening, adhesions or effusion. The diagram in the lower right panel is not considered suggestive of pericardial disease. See text and Figures 3 to 9 for description of the seven patterns. EN = endocardium; P = pericardium; PP = parietal pericardium; REV = intermittent reverberations; VP = visceral pericardium.

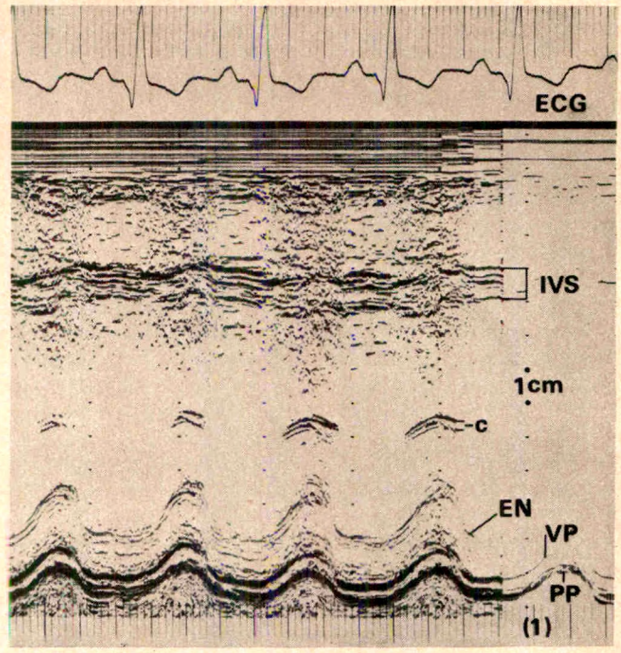

FIGURE 3. Pattern 1 of pericardial thickening. The suggestion of two intense echoes separated by a space in the area of the pericardium is confirmed after the damping maneuver in the right portion of the panel because two intense echoes remain, and the more posterior one is most intense. c = chordae tendineae; ECG = electrocardiogram; EN = endocardium; IVS = interventricular septum; PP = parietal pericardium; VP = visceral pericardium.

underwent heart surgery, cardiac catheterization or autopsy; 96 patients had no further cardiac procedure. Forty-five patients had cardiac surgery, 4 a postmortem examination and 22 cardiac catheterization alone (Fig. 1). A total of 64 patients had right heart catheterization; 58 of these also had a left heart study.

Anatomic Findings

Of the 49 patients who had direct pericardial visualization at surgery or autopsy, 37 patients (76 percent) had pericardial thickening or adhesions. In eight patients (16 percent) no comment was made about the appearance of the pericardium; in three patients (6 percent) no pericardial adhesions were described at surgery but no comment at all was made about the appearance of the pericardium, and in one patient (2 percent) a small pericardial effusion was noted at autopsy but neither pericardial adhesions nor thickening was described. The patterns of pericardial thickening noted in the M mode echocardiogram from the 37 patients with positive anatomic findings were correlated with the anatomic descriptions.

Echocardiographic Patterns

Seven echocardiographic patterns of pericardial thickening or adhesions, or both, were used (Fig. 2).

Pattern 1: This pattern consists of two separate echoes representing visceral and parietal pericardial interfaces that are *exactly parallel* to each other, with a clear space of at least 1 mm between the two layers (Fig. 3). With the damping maneuvers no change occurs in the echo-free space, and the posterior or parietal interface is most intense. At surgery or autopsy, no significant thickening of the pericardial layers was described, but adhesions were noted within the pericardial space between the two layers.

Pattern 2: This pattern is similar to pattern 1. The visceral and parietal pericardial interfaces are represented by two separate *parallel* lines, but this separation is not clearly visualized until the damping maneuver is used (Fig. 4). Without damping, the space between the visceral and parietal pericardial layers is either obscured by punctate echoes or is as dense as the left ventricular posterior wall. With maximal damping the space is virtually echo-free and the posterior or parietal pericardial interface is most intense. This pattern represents dense adhesions or multiple fluid-fibrous interfaces in the material between the pericardial layers.

Pattern 3: At least two separate parallel lines are observed for the visceral pericardium, but the parietal pericardium is represented as a single line. This pattern was often combined with the echocardiographic ap-

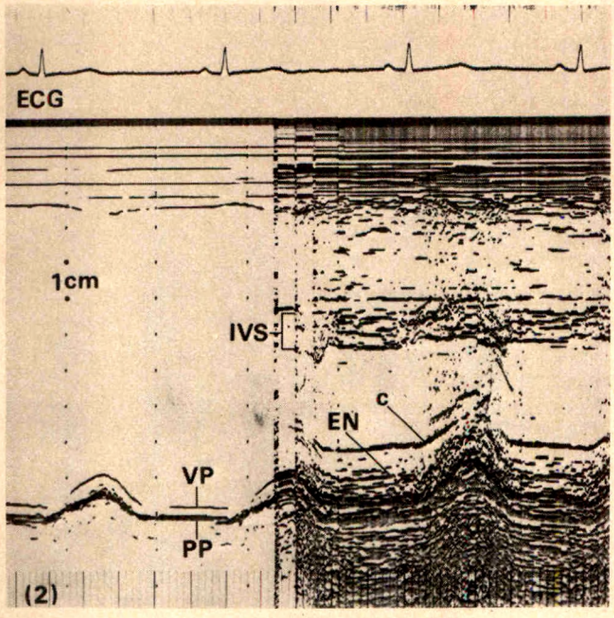

FIGURE 4. Pattern 2 of pericardial thickening. Note the rather intense echoes, in the right portion of the panel, between the visceral (VP) and parietal (PP) echoes identified in the left portion of the panel after the damping maneuver. Abbreviations as in Figure 3.

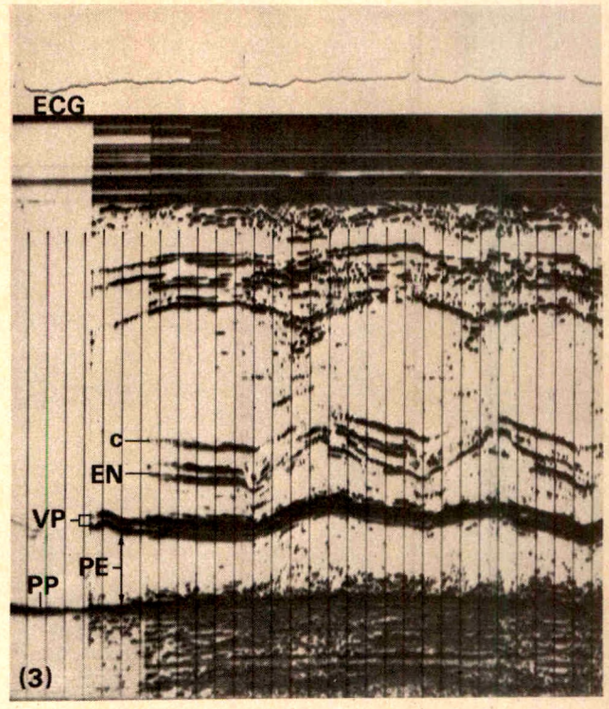

FIGURE 5. Pattern 3 of pericardial thickening. Note the set of echoes representing the visceral pericardium (VP) separated from the flat parietal pericardial (PP) echo. A relatively echo-free space between these sets of lines represents a pericardial effusion (PE). Abbreviations as in Figure 3.

pearance of pericardial effusion, the latter suggested by nonparallel motion of the parietal and visceral interface echoes (Fig. 5). At autopsy or surgery, thickening of the visceral pericardium was described, and in some cases significantly thickened parietal pericardium was noted as well. Hence, a single line in the echocardiogram representing the parietal pericardium cannot exclude anatomic thickening of the parietal pericardium. This pattern often was associated with fluid in the pericardial space.

Pattern 4: Multiple equally dense echoes in the region of the parietal pericardium are interpreted as thickened parietal pericardium (Fig. 6). The visceral pericardium is represented as a single line not significantly thickened. These elements were observed in some cases with the echocardiographic pattern of pericardial effusion: The space behind the visceral pericardium was echo-free and the parietal pericardium was flat. In other cases, the thickened parietal pericardium exhibited exactly the same motion as the visceral pericardium but the pericardial layers were separated by an echo-free space greater than 1 mm. Anatomic examination revealed adhesions between the two layers of the pericardium as well as thickened parietal pericardium without significant thickening of the visceral pericardium.

Pattern 5: Both visceral and parietal interface echoes are represented by separate sets of multiple lines, often in association with the echocardiographic appearance of a pericardial effusion (Fig. 7). Effusion was suggested by nonparallel motion of the sets of echoes, with the most posterior set from the parietal area showing the

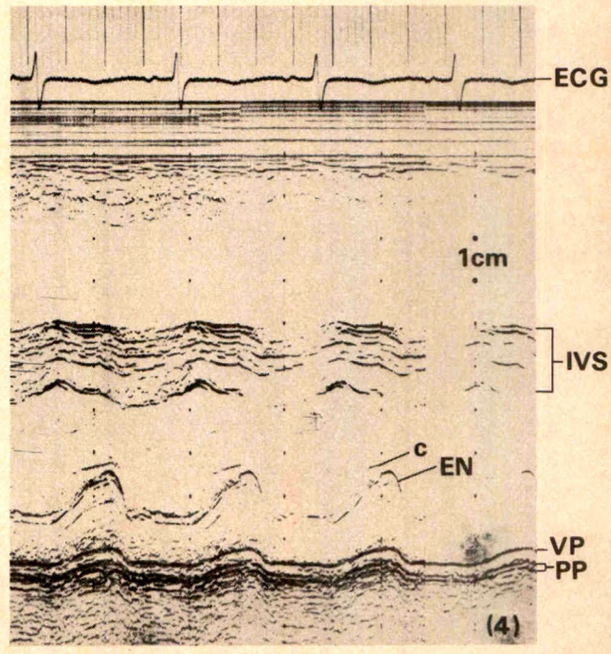

FIGURE 6. Pattern 4 of pericardial thickening. Note the multiple parietal pericardial echoes and the parallel motion of the VP and PP lines. Abbreviations as in Figure 3.

least motion. Anatomically, both pericardial layers were thickened, and a pericardial effusion was often noted.

Pattern 6: The characteristic echocardiographic features of this pattern are the slight systolic anterior motion of the parietal pericardium, which still moves less than the visceral pericardium, and a space between the parietal and visceral echoes which is as echo-dense as, or more dense than, the left ventricular posterior wall at any gain setting (Fig. 8). Anatomically, either pericardial effusion or a "fibrous peel" was described at surgery; thus this pattern did not distinguish among pericardial thickening, adhesions or a small pericardial effusion. The clinical data in many of these cases are compatible with this echocardiographic pattern representing a pericardial effusion that is organizing.

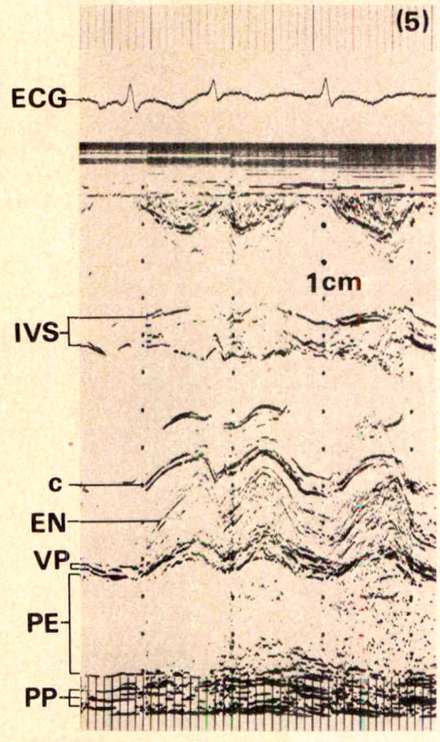

FIGURE 7. Pattern 5 of pericardial thickening. Multiple echoes are seen in the area of the visceral and parietal pericardium. These two sets of echoes are separated by a relatively echo-free space representing pericardial effusion (PE). Abbreviations as in Figure 3.

Pattern 7: Multiple distinct parallel equally dense echoes are visualized in the vicinity of the pericardium with the damping maneuver. However, it is not possible to interpret which lines represent the visceral or parietal interface echoes (Fig. 9). Anatomic description included either fusion of thickened pericardial layers or a severely calcified and fibrotic parietal pericardium with a relatively normal visceral pericardium.

Prevalence of various echocardiographic patterns and correlation with surgical findings: The echocardiogram showed a pattern of pericardial thickening or adhesions recognized as pattern 2 in 34 percent of the 167 cases, and as pattern 1 in 19 percent. In the remaining 47 percent the patterns were equally distributed among patterns 3 through 7. No specific pattern was strictly associated with any individual disease process.

Twenty-four patients were diagnosed as having constrictive pericarditis, and 19 of these underwent pericardiectomy. All patients with constrictive pericarditis had pericardial thickening on echocardiography, but no pathognomonic pattern of constriction was found. Ten patients (42 percent) had effusive constrictive disease. Echocardiographic patterns 3 and 5 were found more frequently in patients with constriction than in those without constriction.

Other echocardiographic features: Other features such as patterns of left ventricular posterior wall and interventricular septal motion, E-F_O slope and percent

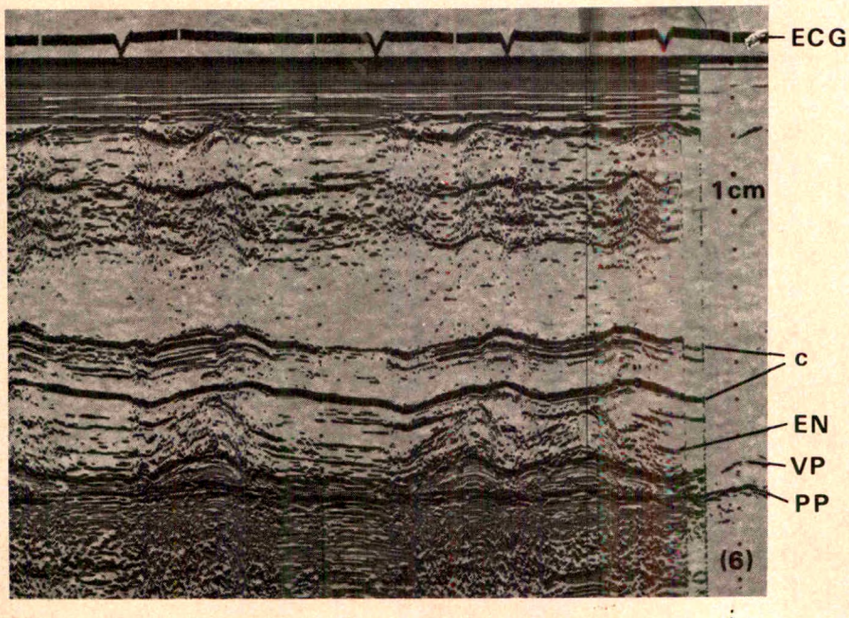

FIGURE 8. Pattern 6 of pericardial thickening. Note the intense echoes in the left portion of the panel between the visceral and parietal lines (seen more clearly in the right portion of the panel). This pattern differs from pattern 2 by the lack of parallel motion of the visceral and parietal echoes. Abbreviations as in Figure 3.

fractional shortening were found to support the diagnosis of pericardial constriction (Table I). Flat left ventricular posterior wall motion in diastole was noted in 9 of 14 patients (64 percent) with constriction without effusion and in 4 of 40 patients (10 percent) with pericardial thickening without constriction who had catheterization. The suggestive interventricular septal motion described by Gibson et al.[3] was noted in 6 of 14 patients (49 percent) with constriction without effusion and in no patient without constriction. A high E-F_O slope was noted in 2 of 14 patients (14 percent) with constrictive pericarditis without effusion but in no patient without constriction. Low percent fractional shortening was found in only 1 of 14 patients (7 percent) with constrictive pericarditis but appeared more commonly in patients with effusive constrictive disease (4 of 10 patients, 40 percent) and in patients without constriction (15 of 40 patients, 38 percent). The atrial emptying index was not of value because a heart rate greater than 85 beats/min, invalidating the measurement, occurred in 20 of 24 patients (83 percent) with constrictive pericarditis or effusive constrictive disease.

Clinical diagnoses associated with pericardial thickening: Table II lists the clinical diagnoses of all patients with pericardial thickening noted on echocardiography. The most common conditions associated with pericardial thickening at this institution are previous cardiac surgery, mediastinal radiation, uremia, history of acute pericarditis and myocardial infarction. Only 22 of 167 patients had no known presumable cause for their pericardial disease. However, 8 of these 22 patients had constrictive pericarditis or effusive constrictive disease. Thus 33 percent of all patients with constriction had pericardial thickening on echocardiography without a known possible cause.

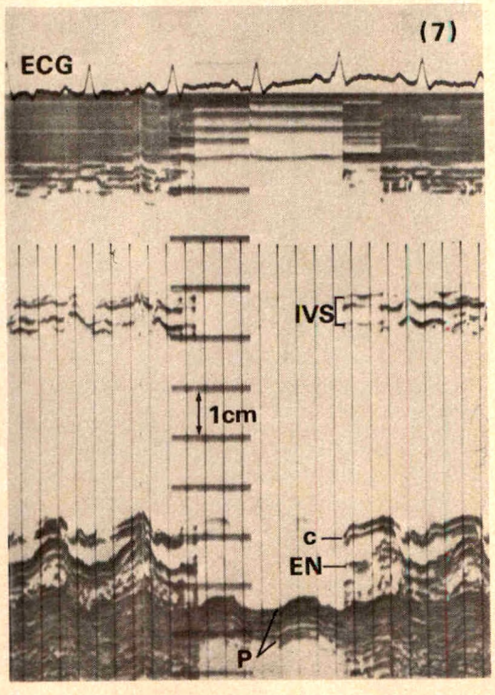

FIGURE 9. Pattern 7 of pericardial thickening. A broad band consisting of multiple intense echoes is present in the area of the pericardium. The arrangement of these echoes does not allow segregation into visceral and parietal echoes. Abbreviations as in Figure 3.

Discussion

Pericardial thickening as noted on echocardiographic examination is relatively uncommon. We found 173 cases at Stanford University Hospital between the years 1972 and 1977. During this period, approximately 9,000 echocardiograms were performed. All patients in the study were listed in the computerized patient data base at this hospital. Although this file is not entirely complete, the patients included represent an otherwise prospectively unselected group of patients with presumptive echocardiographic evidence of pericardial thickening.

Possible limitations of study: This study is a retrospective analysis of echocardiograms showing pericardial patterns not classic for pericardial effusion and originally interpreted as suggesting pericardial thickening. Such a study has several inherent weaknesses. Patients underwent direct cardiac visualization (surgery or autopsy) for a variety of reasons, and surgeons and

TABLE I

Occurrence of Other Echocardiographic Abnormalities in Patients With and Without Constriction

	Pericardial Constriction and No Effusion (no. = 14)	Effusive Constrictive Disease (no. = 10)	No Hemodynamic Evidence of Constriction (no. = 40)
Flat left ventricular posterior wall motion	9	1	4
IVS motion as described by Gibson et al.[3]	6	0	0
E-F_O slope (>11.7 cm/sec)	6	1	0
Low % fractional shortening (<28%)	1	4	15

FS = fractional shortening; IVS = interventricular septal.

TABLE II

The Clinical Diagnosis of 167 Patients With Pericardial Thickening

	no. of Patients	% of Total
Post heart surgery state	31	19
Neoplasm		
With radiation to chest	24	14
In mediastinum, without radiation	3	2
Chronic renal failure with uremia	25	15
Pericarditis (viral, bacterial, parasitic)	17	10
Acute postmyocardial infarct state	14	8
Connective tissue disease	12	7
Rheumatic heart disease	7	4
Cardiomyopathy	7	4
Other*	5	3
Unclassified	22	13

*Recurrent pulmonary embolism, traumatic pericarditis, amyloidosis, atrial septal defect and malignant pericarditis occurred in one patient each.

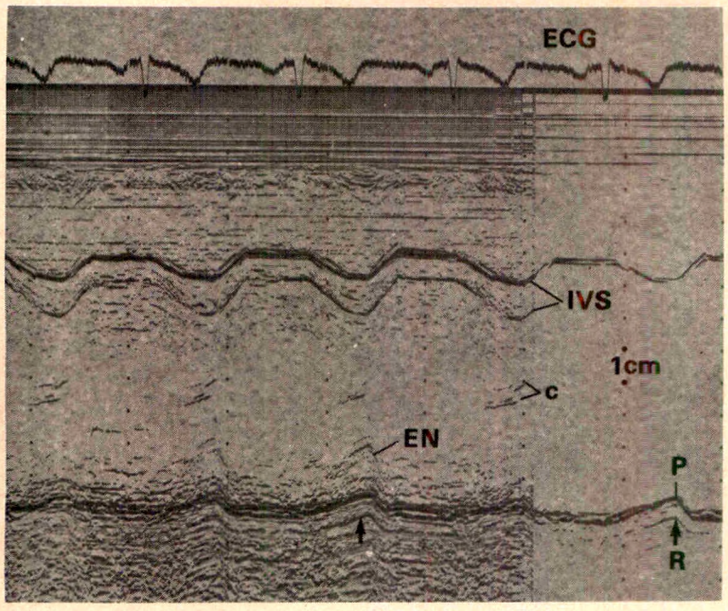

FIGURE 10. Echocardiogram demonstrating reverberations (R) posterior to the strong pericardial echo (P). The presumed reverberations can be seen both before and after the damping maneuver **(arrows)**. This pattern is *not* considered representative of pericardial disease. Abbreviations as in Figure 3.

pathologists did not attempt to describe specifically the appearance of the pericardium. Hence, 8 of the 49 patients with such an anatomic description had case records in which no comments were made about the appearance of the pericardium. Among 96 patients without further cardiac evaluation, the clinical diagnoses and pathologic processes in the majority were compatible with assumed pericardial involvement. However, one cannot determine from our study how many patients had a false positive echocardiographic reading of pericardial thickening or significant anatomic pericardial thickening without an echocardiographic reading of pericardial thickening.

Not all the echocardiograms were recorded with specific attention focused upon the pericardium. A careful echocardiographic examination of the left ventricular cavity with intermittent appropriate damping maneuvers should be performed to evaluate the pericardium. In our experience reverberations behind the pericardium may mimic either pattern 1 or 2 of pericardial thickening (Fig. 2 and 10). This confusion is a result of the high energy long pulses that generate an artifact behind the parietal pericardium. This artifact is eliminated by using the damping maneuver, which provides less absolute energy and permits optimal visualization of the individual echoes reflected from the posterior pericardium. However, reverberation still may occur behind a very strong parietal pericardial interface, even with the low energy short pulses. Therefore, we do not consider multiple low intensity echoes posterior to an intense parietal pericardial interface to represent parietal pericardial thickening (Fig. 2).

When we tried to correlate anatomic findings with the echocardiographic patterns of pericardial thickening we found several incomplete surgical and pathologic reports. We selected the most descriptive and informative notes characterizing the findings in patients with each of the seven echocardiographic patterns.

Clinical significance of various echocardiographic patterns of pericardial thickening: The importance of defining one, two or seven patterns of pericardial thickening is not established, and it can be difficult to assign each echocardiogram to a specific pattern. The pattern may vary if various levels of the ventricle are recorded, just as patchy pericardial involvement may be seen anatomically. However, our study showed that these patterns usually mean anatomic pericardial thickening and adhesions and that they may help to identify the type of pericardial disease present. Use of these criteria in other laboratories may clarify the significance of this classification.

In all cases indexed under constrictive disease in the computer patient data base pericardial thickening with or without pericardial effusion was identified in the echocardiogram. However, our series is too small to claim that all patients with pericardial constriction have a positive echocardiogram for pericardial thickening. The 24 cases of hemodynamically proved constrictive disease represented 14 percent of our total group of 167 patients. Because our institution is a referral center, this prevalence rate of constrictive disease may be unusually high among patients with echocardiographic evidence of pericardial thickening. We found no diagnostic echocardiographic pattern of pericardial thickening for constrictive disease. Patterns 3 and 5, which included a thickened visceral pericardium and frequently included pericardial effusion, were more often seen in patients with effusive constrictive disease than in other groups. This finding supports the concept that the visceral pericardium is a constrictive element along with the pericardial effusion in this subset of cases.

Clinical value of other echocardiographic measurements: In patients without pericardial effusion, other echocardiographic measurements may help to suggest pericardial constriction. A flat left ventricular posterior wall after an early rapid posterior motion in

diastole occurred in more than half of the patients with constrictive pericarditis.[2] This finding may represent early rapid filling of the left ventricle; followed by restriction to further filling. This sign is not specific because it was noted also in patients with no hemodynamic evidence of constriction.

The abnormal interventricular septal motion with a late diastolic anterior displacement did not occur in any patient without constriction and therefore may be a specific (but insensitive) sign of constriction.[3] A high E-F_O slope also occurred only in patients with constriction or effusive constrictive disease; therefore its presence in combination with pericardial thickening suggests pericardial constriction. The atrial emptying index was not helpful, but the percent fractional shortening was more often normal than low in patients with constrictive pericarditis; the reverse was true in patients without constriction. Thus the appearance of pericardial thickening, characteristic left ventricular posterior wall and interventricular septal motion abnormalities and a high E-F_O slope, especially in a patient without known cause of pericardial thickening, strongly suggests constrictive pericarditis.

Clinical implications: Our present criteria for pericardial thickening on M mode echocardiography include several patterns that are consistent with pericardial thickening. It remains unknown whether anatomic pericardial thickening occurs without echocardiographic evidence of pericardial thickening. Echocardiographic findings of pericardial thickening are not equivalent to constrictive pericarditis. Hemodynamic diagnosis of constrictive disease is associated with the echocardiographic finding of pericardial thickening, but there is no specific pattern of pericardial thickening pathognomonic of constrictive disease. Careful analysis of interventricular septal motion, left ventricular posterior wall motion and E-F_O slope in patients with suspected constriction can provide additional information supporting the diagnosis of constrictive pericarditis.

References

1. **Horowitz MS, Schultz CS, Stinson EB, et al:** Sensitivity and specificity of echocardiographic diagnosis of pericardial effusion. Circulation 50:239–247, 1972
2. **Feigenbaum H:** Echocardiography. Philadelphia, Lea & Febiger, 1976, p 419–446
3. **Gibson TC, Grossman W, McLaurin LP:** An echocardiographic study of the interventricular septum in constrictive pericarditis. Br Heart J 38:738–743, 1976
4. **Sanders WJ, Sanders GR, Harrison DC, et al:** A computerized database system for medical research. Rotterdam, Proc IEEE Symposium, 1977
5. **Strunk BL, London EJ, Fitzgerald J, et al:** The assessment of mitral stenosis and prosthetic mitral valve obstruction using the posterior aortic wall echocardiogram. Circulation 55:885–891, 1977
6. **Valdez R, Motta J, Martin R:** Survey of a normal population with the echocardiogram (abstr). Am J Cardiol 277:39, 1977
7. **Hancock EW:** Subacute effusive-constrictive pericarditis. Circulation 43:183–192, 1971
8. **Popp RL:** Echocardiographic assessment of cardiac disease. Circulation 54:538–552, 1976

Carotid Sinus Hypersensitivity and Syncope

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Hyperactivity of the carotid sinus reflex is common in older men. However, an unequivocal diagnosis of carotid sinus syncope is difficult to establish because the symptoms are nonspecific, and both hyperactivity of the carotid sinus reflex and syncope are common. Twenty-one men were evaluated for episodes of lightheadedness or syncope, or both, associated with a hypersensitive carotid sinus reflex. Seventeen patients had the cardioinhibitory type, two the vasodepressor type and two both the cardioinhibitory and vasodepressor types. Patients with the cardioinhibitory type benefited from the insertion of a permanent pacemaker if they had multiple episodes of syncope. A history of syncope associated with some event capable of stimulating the carotid sinus was also helpful in selecting patients for pacemaker treatment. The combination of the cardioinhibitory and vasodepressor types may be missed unless carotid sinus stimulation is repeated after the administration of atropine. The results of electrophysiologic studies in 17 patients with the cardioinhibitory type suggest that intrinsic sinus nodal dysfunction is not the major cause for asystole after carotid sinus stimulation.

The carotid sinus has an important role in the normal reflex regulation of heart rate and peripheral vascular tone. An increase in intrasinusal tension produces a slowing of the heart rate and a decrease in systemic arterial blood pressure.[1] Mechanical stimulation of the carotid sinus in normal subjects results in a mild slowing of the heart rate and an insignificant decrease in arterial blood pressure.[2] Hyperactivity of the carotid sinus has been recognized and is associated with an exaggeration of the normal response. In some persons the hemodynamic response to carotid stimulation is so pronounced that clinical symptoms of syncope and profound hypotension result.

The hyperactive carotid sinus reflex is found in approximately one third of older men with coronary atherosclerotic and hypertensive heart disease.[3–5] Syncope or a transient clouding of consciousness without syncope is a common symptom in these patients. When spontaneous syncope and a hyperactive carotid sinus reflex coexist, it is tempting to assume that the hyperactive reflex is the cause of syncope. However, its presence may be coincidental because most patients with a hyperactive carotid sinus reflex are asymptomatic.[3,4] It may be difficult to know whether the hyperactive reflex is responsible for the symptoms.

There is a paucity of published information about the selection of patients for therapy directed toward the hyperactive reflex. Therefore, the present study was undertaken for the following purposes: (1) to examine the clinical symptoms and response to treatment of patients with hyperactive carotid sinus reflex and syncope or near syncope, in an attempt to improve the accuracy of diagnosis; and (2) to assess sinoatrial nodal and atrioventricular (A-V) nodal function in these patients with atrial pacing and administration of intravenous atropine.

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Methods

Patients: From 1971 to 1976 patients seen by the Cardiology Services at the Atlanta Veterans Administration Hospital and Emory University Hospital for evaluation of syncope or near syncope of unknown cause were tested with external carotid sinus stimulation unless they had cerebral vascular disease or other contraindications to this procedure. Twenty-one men were considered to have hypertensive carotid sinus. The patients were considered to have syncope of unknown cause if the history, physical examination, resting electrocardiogram, neurologic consultation or, in 71 percent of cases, continuous 24 hour ambulatory electrocardiographic monitoring did not explain the symptoms. Eight of the nine patients with cardioinhibitory carotid sinus hypersensitivity experiencing only dizziness (Patients 10 to 18, Table I) had 24 hour ambulatory electrocardiographic monitoring. Digitalis, propranolol and other drugs known to affect sinoatrial nodal function were discontinued 1 week before carotid sinus stimulation.

Carotid sinus stimulation: This was performed initially with the patient supine and was repeated with the patient sitting and standing when vasodepressor syncope was suspected. The carotid sinus was massaged gently for approximately 5 seconds, first on one side and then on the other, while an electrocardiogram was recorded and blood pressure monitored. If there was no response, manual pressure was increased for an additional 5 seconds. Cardioinhibitory carotid sinus hypersensitivity was defined as ventricular asystole for more than 3 seconds during carotid sinus stimulation. This definition was proposed by Franke[2] and is accepted by others.[3] The vasodepressor type of carotid sinus hypersensitivity was considered to exist when there was a decrease in systolic blood pressure of 50 mm Hg or greater with no associated cardiac slowing, or when the decrease in systolic blood pressure was

TABLE I

Clinical Features of 21 Patients

Case no.	Age (yr)	Type of CSH	Symptoms; Inciting Events	Associated Disease	ECG	CSS (sec)	Treatment	Clinical Observation (mo.)
1	66	CI	Multiple syncope; micturition	CASHD	LAD	R,4 asystole	Pacemaker	No syncope or dizziness (8)
2	63	CI	Multiple syncope	CASHD, DM	ST-T	L,3.1 asystole	Pacemaker	No syncope or dizziness (24)
3	47	CI	Multiple syncope; shaving	CASHD, SAH	LAD	R,3.5 asystole	Pacemaker	No syncope or dizziness (45)
4	50	CI	Multiple syncope; sneezing, head turning		WNL	R,3.1 asystole	Pacemaker	No syncope or dizziness (41)
5	63	CI	Multiple syncope; shaving	CASHD	IMI	L,6 asystole	Pacemaker	No syncope, rare dizziness (7)
6	57	CI	Multiple syncope	Hyperthyroid treatment	1° A-V block	R,3.8 asystole	Pacemaker	No syncope or dizziness (27)
7	63	CI	Multiple syncope; looking up	CASHD	LVH	R,3.4 asystole	Pacemaker	No syncope, rare dizziness (26)
8	47	CI	Multiple syncope; shaving	CASHD, SAH	IMI	L,6 asystole	Pacemaker	No syncope or dizziness (12)
9	51	CI, VD	Multiple syncope; neck pressure	CASHD	IMI	R,3.6 asystole	Pacemaker	Syncope (1 episode), BP decrease with CSS (5)
10	65	CI	Dizziness	CASHD	IMI	L,3.7 asystole	. . .	Dizziness and visual blurring, VBI (57)
11	47	CI	Dizziness	CASHD, SAH	IMI	R,3.3 asystole	. . .	No syncope (24)
12	75	CI	Syncope (1 episode); dizziness	CASHD	LAD	L,3.7 CHB	. . .	Dizziness, VBI (2)
13	60	CI	Dizziness	CASHD, SAH	IMI	R,5.4 asystole	. . .	No syncope (39)
14	84	CI	Postural collapse; no syncope	SAH	LVH	L,5.4 asystole	. . .	No syncope (12)
15	54	CI	Fading out; no syncope	CASHD, DM	IMI	L,6.1 asystole	. . .	No syncope, transient confusion, normal pulse, BP (48)
16	62	CI	Dizziness	CASHD, DM, SAH	IMI, LVH	R,6 asystole	. . .	No syncope (50)
17	68	CI	Dizziness; head turning	CASHD, SAH	LBBB	R,6 asystole	. . .	Lost to follow-up
18	76	CI	Dizziness	DM	WNL	R,4 asystole	. . .	Lost to follow-up
19	64	VD	Dizziness; neck extension	SAH	WNL	Decrease in BP	Stop all medication	Episodes less frequent (12)
20	76	CI, VD	Dizziness with exercise	Mitral regurgitation	1° A-V block	R,6 asystole	Pacemaker, mineralocorticoid	Orthostatic dizziness controlled by mineralocorticoid (21)
21	59	VD	Multiple syncope; head turning; tight collar	Aortic stenosis	WNL	Decrease in BP	Pacemaker, irradiation	No syncope for 61 mo postirradiation (89)

A-V = atrioventricular; BP = blood pressure; CASHD = coronary atherosclerotic heart disease; CHB = complete heart block; CI = cardioinhibitory; CSH = carotid sinus hypersensitivity; CSS = carotid sinus stimulation; DM = diabetes mellitus; IMI = inferior myocardial infarction; L = left; LAD = left axis deviation; LBBB = left bundle branch block; LVH = left ventricular hypertropy; R = right; SAH = systemic arterial hypertension; ST-T = ST-T wave change; VBI = vertebral basilar arterial insufficiency; VD = vasodepressor; WNL = within normal limits.

greater than 30 mm Hg and the patient's symptoms were reproduced.[2]

Electrophysiologic study: This was performed in 17 patients with cardioinhibitory carotid sinus hypersensitivity. Informed consent was obtained. The patients were studied in the resting nonsedated state. At the time of study, all cardioactive drugs had been discontinued for at least 1 week. A bipolar electrocatheter was passed under fluoroscopic control by way of an antecubital vein into the right atrium and positioned so that the electrodes were at the junction of the right atrium and superior vena cava. Atrial pacing was begun at a rate of 10 beats/min faster than the spontaneous sinus rate and was increased every 2 minutes by increments of 10 beats/min until a rate of 150 beats/min was achieved. His bundle electrograms were obtained with the technique of Sherlag et al.[6] in six patients. After the studies, 1 mg of atropine sulfate was administered intravenously in 14 patients, and carotid sinus stimulation was repeated in the same manner.

At the rate of maximal suppression, the sinus nodal recovery time was measured from the last atrial paced beat to the following sinus beat. Secondary pauses after the termination of rapid atrial pacing were measured if these pauses exceeded the length of the first escape cycle (one patient). The corrected sinus recovery time was obtained by subtracting the spontaneous sinus cycle length before pacing (average 10 cycles) from the sinus nodal recovery time. The corrected sinus recovery time was considered abnormal if the interval exceeded 525 msec.[7] Atrioventricular (A-V) nodal conduction was considered abnormal if second degree A-V block occurred at pacing rates of less than 130 beats/min.[8]

Results

Clinical features: The 21 men evaluated for episodes of lightheadedness or syncope associated with carotid sinus hypersensitivity ranged in age from 47 to 84 years (mean 62) (Table I). Seventeen patients had the cardioinhibitory type of hypersensitive carotid sinus reflex, two the vasodepressor form and two both the cardioinhibitory and vasodepressor types. Most of the 21 patients had heart disease; 14 had coronary atherosclerotic heart disease, diagnosed from a history of angina pectoris (14 patients), prior myocardial infarction (9 patients) or coronary arteriography (4 patients). Three patients had had coronary bypass surgery. Only two men had no clinical evidence of associated organic heart disease, but neither had had cardiac catheterization or coronary arteriography. Electrocardiographic evidence of prior inferior myocardial infarction was found in 8 of the 14 patients with coronary atherosclerotic heart disease. No patient had documented spontaneous sinoatrial block. The one patient with paroxysmal atrial tachyarrhythmia had been treated for hyperthyroidism 24 years earlier but was euthyroid at the time of examination.

Cardioinhibitory type with syncope: Patients 1 to 9 (Table I) with the cardioinhibitory type each had had five or more episodes of syncope and also numerous episodes of near syncope. Their symptoms occurred when they were sitting or standing and never while recumbent. Seven of these nine patients recalled some event that may have been important in precipitating syncope. A history of hyperextension of the neck when shaving, looking at the sky, head turning or head turning on backing up in a motor vehicle, local pressure on the neck, micturition or sneezing suggested possible precipitating factors. These possible causal factors preceded only the minority of episodes, and in some instances the history of these events was obtained only after repeated questioning. A history of a precipitating event was not obtained in two patients who could not remember events prior to syncope.

Three patients had syncope while driving. One of these patients had several serious accidents while backing up his truck. Two patients had postsyncopal chest pain typical of myocardial ischemia. One patient had a marked increase in frequency of syncope while taking propranolol.

The duration of symptoms before the demonstration of carotid sinus hypersensitivity in these nine patients was 1 to 46 months (mean 17 months). Three patients were followed up for 8, 26 and 48 months before pacemaker implantation. Tincture of belladonna was tried in all three but was beneficial only temporarily. Serious side effects, including visual blurring and urinary retention, necessitated stopping the drug or reducing the dose to a level that no longer prevented symptoms. During the observation period before pacemaker insertion, two patients were asymptomatic for 16 and 37 months, respectively, but both had later recurrence of multiple episodes of syncope.

Patients 1 to 9 were treated with a demand cardiac pacemaker: These patients have been followed up for 5 to 45 months (mean 22) since pacemaker implantation. Syncope has not recurred in eight of the nine patients. Patient 9 had a single episode of syncope while eating breakfast 4 months after pacemaker insertion. Evaluation at that time showed the pacemaker to be functioning normally. The systemic arterial blood pressure was 120/82 mm Hg in the sitting position, but decreased to 80/70 mm Hg with gentle right carotid stimulation. During stimulation the pacemaker rate was unaltered at 70 beats/min. The patient noted transient dizziness coincident with the decrease in blood pressure. He appears to have both cardioinhibitory and vasodepressor hypersensitivity and, if his symptoms continue, further therapy will be necessary. Although syncope has not recurred since pacemaker insertion, two of these patients have occasional episodes of lightheadedness while standing. Orthostatic hypotension appears to be the cause of symptoms in one patient and the cause is unknown in the other.

Three of the nine patients had significant complications related to the insertion of a permanent cardiac pacemaker. One patient had a perioperative subendocardial myocardial infarction, one had the postpericardiotomy syndrome and required hospitalization for treatment of a large pericardial effusion and one had a perioperative myocardial infarction when the pacemaker was implanted at the time of coronary bypass surgery.

Cardioinhibitory type without syncope: Patients 10 to 18 (Table I) did not have syncope (except for a single episode in one man) but had a spectrum of complaints involving transient clouding of consciousness.

Unlike most of the patients requiring pacemaker therapy, only one of these nine patients could recall a precipitating event capable of stimulating the carotid sinus. Seven of these nine patients have been followed up for an average of 33 months, and none have experienced syncopal episodes. During the follow-up period a neurologic consultant diagnosed vertebral basilar arterial insufficiency in addition to carotid sinus sensitivity in two patients; the symptoms typical of the insufficiency were not apparent from the initial evaluation. Five patients have noted a decrease or disappearance of their symptoms, for which no satisfactory explanation was found.

Vasodepressor or mixed type: Patients 19, 20 and 21 have vasodepressor or both vasodepressor and cardioinhibitory carotid hypersensitivity; they will be discussed individually.

Patient 19: For the preceding 5 years, this 64 year old man had experienced dizziness without complete loss of consciousness when he extended his neck and lifted his arms to place articles on shelves in a warehouse. At the time of the initial examination, he was taking hydralazine, 40 mg/day, for arterial hypertension. The maximal pause ever recorded on his electrocardiogram during carotid sinus stimulation was 1.4 seconds. The recumbent blood pressure was 140/80 mm Hg and decreased to 125/70 mm Hg on standing. During right carotid sinus stimulation, the blood pressure decreased to 80/60 mm Hg during sitting and 70/50 during standing, and the patient's spontaneous symptoms were reproduced. On repeat testing after discontinuation of hydralazine, blood pressure was 150/82 mm Hg while he was recumbent, 130/80 during standing and 98/80 during standing with right carotid sinus stimulation. The patient had no symptoms when blood pressure was 98/80 mm Hg. During the past year the patient continued to have symptoms at work, but they occurred less frequently. In the future more definitive therapy may be needed. The reflex decrease in systolic blood pressure did not exceed 50 mm Hg when all medications were discontinued and therefore did not meet the criteria proposed by Franke[2]; however, the vasodepressor response to carotid stimulation probably played a major role in the genesis of this patient's symptoms.

Patient 20: This 76 year old man with both cardioinhibitory and vasodepressor carotid sinus hypersensitivity was first seen because of three episodes of dizziness with near syncope during exercise. The blood pressure was 150/70 mm Hg with the patient recumbent and 140/70 while he was sitting. Right carotid sinus stimulation produced a 6 second period of asystole. A permanent demand pacemaker was inserted. One month later, the patient complained of dizziness while walking. Blood pressure was 120/80 mm Hg in the recumbent and standing positions, respectively. Right carotid sinus stimulation performed with the patient seated resulted in a decrease in blood pressure to 80/60 mm Hg with a pacemaker-driven heart rate of 71 beats/min. The patient's symptoms of dizziness were duplicated during right carotid sinus stimulation. He was given fludrocortisone (Florinef®) acetate, 0.1 mg/day, and has been free of dizziness for 1 year, except for a few weeks when the medication was inadvertently discontinued. The fludrocortisone acetate increased the blood pressure to 160/100 and 150/100 mm Hg in the recumbent and standing position, respectively.

Patient 21: This 59 year old school teacher experienced syncope when he turned his head to look at the back of his classroom. He had stopped wearing neckties because he associated wearing a tight collar with spells of dizziness. A permanent demand pacemaker had been inserted 9 months earlier because of three syncopal attacks that were assumed to be secondary to a bradyarrhythmia. Asystole had not been documented, however, and carotid sinus stimulation was not performed before the pacemaker insertion. The pacemaker was found to be functioning normally. Aortic valve stenosis of mild to moderate severity was detected. Bilateral carotid arteriograms were normal. Blood pressure was 130/80 mm Hg in the standing position. During right carotid sinus stimulation Korotkoff sounds could not be heard, and presyncopal symptoms developed. The patient was advised not to wear tight collars or turn his head abruptly, but syncopal episodes continued, some associated with singing or head turning. Radiation therapy to a tissue dose of 900 roentgens was administered to both the right and the left carotid sinus. One year after the radiation therapy, the patient's symptoms recurred. Syncope was induced by head turning but not by exercise. Right carotid stimulation performed with the patient seated produced a decrease in systolic blood pressure from 130 to 82 mm Hg, and the patient became dizzy. There was no change in systolic blood pressure during left carotid stimulation. The right carotid sinus was again radiated, with a tissue dose of 1,200 roentgens yielding a total dose to the right carotid sinus of 2,100 roentgens. Over the ensuing 5 years, the patient has had no syncope or near syncope, and right or left carotid sinus stimulation does not alter blood pressure.

Two years after the second course of radiation therapy, the patient had congestive heart failure due to aortic stenosis. Cardiac catheterization confirmed the presence of severe aortic stenosis and demonstrated normal coronary arteries. The stenotic aortic valve was replaced. Although the presence of aortic stenosis surely decreased the patient's ability to compensate for decrease in peripheral arterial resistance induced by the carotid sinus reflex, the valve lesion was probably not the major cause of syncope because: (1) syncope was incited by head turning and carotid sinus stimulation rather than by exercise, and (2) the symptoms were abolished by the carotid sinus radiation a full 2 years before the replacement of the stenotic aortic valve.

Electrophysiologic studies: In the 17 patients with cardioinhibitory hypersensitive carotid sinus reflex, the corrected sinus nodal recovery time was less than 525 msec in 14 patients and greater than 525 msec in 3 patients (Table II). The rate of atrial pacing that produced maximal sinoatrial nodal suppression varied from 76 to 150 beats/min. Of the eight patients treated successfully with pacemakers who consented to be studied, seven had a normal and one a prolonged corrected sinus nodal recovery time. The single patient with prolonged recovery time had sinus bradycardia and paroxysmal atrial fibrillation and flutter. Atrioventricular Wenckebach periods developed at a paced atrial rate greater than 130 beats/min in 13 patients and less than 130 beats/min in 3. After the administration of 1 mg of atropine, 1:1 A-V conduction was present at a pacing rate of 140 beats/min or less in the later three patients.

His bundle recordings were obtained in six patients. The H-V intervals were 55 msec or less, and the A-H intervals ranged from 65 to 90 msec. The effect of 1 mg of atropine on corrected sinus nodal recovery time was studied in two of the three patients with prolonged recovery time. The recovery time was normal in one patient and could not be determined in the second patient

TABLE II

Results of Physiologic Studies

Case no.	Resting Sinus Rate (beats/min)	Sinus Nodal Reovery Time (msec)	Connected Sinus Recovery Time (msec)	Paced Rate at Maximal Suppression (beats/min)	Sinus Rate Before Atropine (beats/min)	Heart Rate After Atropine (beats/min)	Rate of A-V Wenckebach Conduction (beats/min)
1	70	920	60	130	...	...	>130
2	86	880	182	150	69	120	>150
3	67	1090	190	123	77	98	>150
4	60	1280	280	120	58	79	>130
5	80	1040	290	143	79	88	>140
6	48	1900	650	90	46	58	>130
7	57	1550	490	145	70	75	105
8	81	860	120	97, 150	79	88	>150
10	58	1560	530	76	60	114	94
11	76	1040	250	105	...	...	>138
12	78	1180	410	90	69	109	>140
13	60	1150	150	138	75	100	138
14	56	1850	780	148	56	88 (junctional)	>140
		2530 (beat #2)	1460				
15	80	1130	380	144	76	92	>145
16	77	1150	370	133	60	75 (junctional)	...
17	80	1080	330	143	80	90	>143
18	60	1240	240	107	...	...	107

A-V = atrioventricular.

because the postpacing pause was terminated by an A-V junctional beat.

Atropine (1 mg) was given to 14 patients. The post-atropine pulse rate was less than 90 beats/min in seven patients (five with sinus rhythm and two with A-V junctional rhythm), and in the other seven patients the sinus rate was 90 beats/min or greater.

Discussion

Cardioinhibitory Type

Precipitating causes of syncope: Our results in patients with the cardioinhibitory type of carotid sinus hypersensitivity suggest that the patient's history may be of value in selecting candidates for aggressive therapy. All of our patients whose syncope was abolished by a cardiac pacemaker had multiple syncopal episodes and many additional episodes of near syncope. These symptoms always occurred when the patient was standing or seated. Most patients could recall a precipitating event associated with episodes of syncope, although the majority of syncopal episodes were not initiated by a trigger mechanism. A few patients were unable to give a history of a precipitating event because they were unable to remember events before the episode. Most of the factors that produced syncope were maneuvers inducing direct pressure or tension on the carotid sinus. It should be noted that head turning or neck extension may produce, in addition to carotid sinus stimulation, mechanical impairment of blood flow through the vertebral arteries.[9] Activities other than those that produce extravascular stimulation of the carotid sinus region can induce clinical symptoms in certain predisposed persons. In some patients coughing, sneezing and straining at stool have induced spontaneous syncope.[4,10] Syncope associated with micturition and intense sneezing was noted in our series.

Reproducibility of symptoms by carotid sinus stimulation: The need to reproduce the exact symptoms with carotid sinus massage before instituting treatment is controversial.[3,10,11] In most of our patients we were unable to reproduce an identical symptom complex with carotid sinus stimulation. All patients noted dizziness during the period of asystole; however, a complete loss of consciousness occurred in only one patient, probably because carotid sinus stimulation was performed with the patient recumbent and was stopped when a pause was noted in the electrocardiogram. The additional information that might be obtained by having the patient sit or stand during manual stimulation of the carotid sinus or by continuing stimulation until syncope occurs, may not justify the risk of inducing serious cerebral or cardiac ischemia. In addition, in some patients with no spontaneous symptoms the carotid sinus may be sensitive and massage may precipitate unconsciousness.

Natural history: Little is known about the natural history of the cardioinhibitory form of hypersensitivity. Because Patients 1 to 9 had had symptoms an average of 17 months before examination and three patients were followed up before pacemaker insertion, we observed the clinical course of these patients for a considerable period of time. In general, the frequency of spontaneous syncope seemed to wax and wane, and some patients were free of symptoms for more than a year. We were unable to detect any factors such as variation in the severity of angina pectoris or hypertension to account for the variability in spontaneous attacks. However, syncope did recur and no patient had a permanent resolution of his symptoms without defi-

nite treatment. During symptom-free periods, the response to carotid sinus stimulation was sometimes normal. Fluctuation in carotid sinus sensitivity has been noted by others.[3,10]

Patients without syncope: In the patients with episodes of clouding of consciousness rather than syncope, a history of precipitating factors was rarely obtained on the initial or follow-up visits. In seven of the nine patients followed up for an average of 33 months syncope did not develop. Follow-up examination, including a repeat history, supine and standing blood pressure measurements and treadmill exercise testing, was useful in establishing a diagnosis in a few patients. Occasionally a patient's symptoms disappeared spontaneously, although in others they continued but defied explanation. Hypersensitivity of the carotid sinus reflex may have contributed to symptoms in these patients without true syncope, but it was probably not a major factor.

Vasodepressor or Mixed Type

The effects of carotid sinus stimulation on the heart and the peripheral vasculature appear to be independent of each other.[12] Atropine abolishes slowing of the heart rate but does not prevent a decrease in systemic blood pressure.[1,12,13] The decrease in blood pressure results from inhibition of sympathetic vasoconstrictor nerves and possibly activation of cholinergic sympathetic vasodilator fibers.[1] Epinephrine administered parenterally may prevent the hypotension.[3] The clinical symptoms of the vasodepressor type are the same as those occurring in the cardioinhibitory form, but the episodes may be extended in the vasodepressor form because the decrease in blood pressure generally lasts longer than the bradycardia.[1,12]

Patients having vasodepressor or both cardioinhibitory and vasodepressor hypersensitivity are especially challenging. Although one review[1] of the hyperactive carotid sinus reflex states that various reflex types often occur in the mixed form, it is difficult to find published examples of such patients. Two patients in our group appear to demonstrate both vasodepressor and cardioinhibitory types.

The definition for the vasodepressor type of hyperactive reflex proposed by Franke[2] is a decrease in systolic blood pressure of 50 mm Hg or greater. The systolic blood pressure did not always decrease 50 mm Hg or more in our patients with the vasodepressor type, but symptoms were reproduced in all patients. The response may have been blunted because blood pressure was determined in the sitting position in two patients and carotid stimulation was terminated on the appearance of symptoms. However, it appears that vasodepressor hypersensitive carotid sinus reflex was important in the genesis of symptoms in our patients.

Diagnosis of vasodepressor type in presence of cardioinhibitory type: It is distressing to find patients who continue to have syncope or near syncope after pacemaker treatment for cardioinhibitory carotid sinus hypersensitivity. It is possible that the carotid hypersensitivity and syncope are unrelated and that the cause of the syncope has been missed. A second possibility is that the patient has both the cardioinhibitory and vasodepressor types of carotid hypersensitivity and that, despite the prevention of bradycardia by the pacemaker, the reflex decrease in blood pressure continues to produce symptoms. This combination appears with sufficient frequency to warrant screening for the vasodepressor type in all patients with the cardioinhibitory form. If carotid sinus stimulation provokes cardiac asystole for longer than 3 seconds, 1 mg of atropine should be given intravenously, and the carotid sinus stimulation should be repeated within 5 minutes with the patient seated. If retesting results in a decrease in blood pressure despite the maintenance of a normal heart rate, the patient may be assumed to have vasodepressor as well as cardioinhibitory carotid sinus hypersensitivity.

Treatment

Indications for treatment: A hyperactive carotid sinus reflex that does not cause symptoms requires no treatment. The question of therapy occurs when a patient has repeated episodes of syncope or near syncope, and the common causes of syncope have been excluded. If the patient is taking any drug that affects cardiac pacemaker activity or the capacitance or resistance vessels, therapeutic decisions should be deferred and carotid sinus stimulation repeated when the effects of the drug have dissipated. Digitalis was demonstrated to increase carotid sinus neural discharge for a given change in carotid sinus pressure.[14] We saw one patient, not included in this report, who had syncope and a 3.4 second sinus pause with carotid sinus stimulation only while taking propranolol. The hyperactive carotid reflex and symptoms of syncope disappeared when propranolol was discontinued. Drugs that decrease intravascular blood volume or peripheral arterial resistance or that increase venous capacitance may enhance the hypotensive response to carotid stimulation in a patient with the vasodepressor type of hyperactive carotid sinus reflex.

Patients with cardioinhibitory hypersensitivity who have repeated spontaneous episodes of syncope should be treated. If syncope is precipitated by a maneuver that produces mechanical stimulation of carotid arteries or by a vagal reflex activated from some other site, a reflexly induced cardiac asystole is probably responsible for the symptoms. Observations in several of our patients suggest that spontaneous syncope may disappear for months or even a year but often recurs later. The long-term follow-up of more patients is necessary to determine whether these findings represent the natural history of cardioinhibitory hypersensitivity. The risk of syncope while driving a vehicle or working in certain situations usually necessitates treatment whenever the diagnosis is fairly certain. Patients who have episodes of clouding of consciousness without a known inciting event can, according to our experience, be followed up without therapy.

Cardiac pacemaker implantation: The preferred treatment for cardioinhibitory induced syncope is im-

plantation of a demand cardiac pacemaker. Pacemaker treatment is highly successful, and the results are superior to those reported in any other form of therapy.[1,10,13,15,16] Only about two thirds of patients are free of symptoms after radiation therapy or surgical denervation of the carotid sinus.[1,16] Large doses of anticholinergic drugs are often poorly tolerated and may not abolish symptoms.[15]

Treatment of vasodepressor or mixed types: The best treatment for vasodepressor or mixed vasodepressor and cardioinhibitory carotid hypersensitivity remains to be established. Some milder cases of the vasodepressor form may respond to simple measures, such as increasing blood volume with mineralocorticoids. Severe vasodepressor or mixed vasodepressor cardioinhibitory may require treatment with either radiation therapy or surgical denervation of the carotid sinus. In one of our patients, a total tissue dose of 2,100 roentgens was required to abolish the reflex decrease in blood pressure. This dose is substantially higher than that recommended previously.[16] Carotid sinus denervation with periarterial stripping or the use of electrical nerve stimulation to facilitate the search for sensitive areas on the carotid sinus and surrounding nerves may improve the results of surgical therapy.[17,18]

Electrophysiology

Some authors[19,20] consider carotid sinus hypersensitivity to be part of the "sick sinus node" syndrome. Our results and those of others[11] suggest that carotid sinus hypersensitivity and sick sinus syndrome are separable entities but that both may occur in the same patient. In contrast to patients with the sick sinus syndrome, only one of our patients had paroxysmal atrial tachyarrhythmia alternating with sinus bradycardia (bradycardia-tachycardia syndrome), and no patient had electrocardiographic documentation of type I or II sinoatrial block.

Sinus nodal function: Only 3 of our 17 patients (18 percent) with the cardioinhibitory type of hypersensitivity had a corrected sinus nodal recovery time greater than 525 msec. One of these three patients had abnormal prolongation of a cycle after the first postpacing cycle. Although electrophysiologic testing of sinus nodal function by atrial pacing with determination of corrected sinus nodal recovery time is not a definitive test for separating normal from abnormal sinus nodal function, the incidence rate (18 percent) in our patients of a prolonged corrected sinus nodal recovery time or secondary postpacing pauses was considerably less than the rate reported in patients with symptomatic sinus nodal dysfunction.[21,22] Rosen et al.[8] reported a high incidence rate of A-V conduction defects in patients with sinus nodal dysfunction. Atrioventricular conduction appeared normal in 81 percent of our patients. The results of sinus nodal recovery time in our patients were of little value in selecting patients for pacemaker therapy.

Pathophysiology: The pathophysiology of cardioinhibitory hypersensitivity and the site from which it arises are unknown. The carotid sinus receptors or reflex afferents, the autonomic centers of the brain stem and the efferent limb of the reflex arc have all been proposed as sites of hypersensitivity.[3–5,12,23] A combination of abnormalities at multiple sites is also possible. Changes in the efferent limb of the reflex have received the greatest attention because a hypersensitive carotid sinus reflex is commonly associated with organic heart disease. The cardioinhibitory response to carotid sinus stimulation was demonstrated to increase in experimental animals by myocardial hypoxia and chronically studied unilateral vagotomy.[5,24] Chronically, vagotomy may increase sensitivity to acetylcholine because of degeneration of postganglionic fibers.[24]

Events in the heart that account for prolonged asystole have not been determined. Our data suggest that a disorder of sinus nodal automaticity or sinoatrial conduction is not the major reason for asystole. The corrected sinus nodal recovery time was normal in 82 percent of the patients with the cardioinhibitory type of carotid sinus hypersensitivity in our series and in that reported on by Hartzler and Maloney.[11]

Increased vagal tone is a more likely explanation, with several possible mechanisms in effect: (1) a high level of resting vagal tone, (2) hyperresponsiveness to acetylcholine, (3) excessive release of acetylcholine, and (4) inadequate cholinesterase activity. A high level of resting vagal tone seems unlikely because atropine did not produce an excessive increase in pulse rate. The heart rate remained less than 90 beats/min in 50 percent of our tested patients. Hyperresponsiveness to acetylcholine is another possibility.[25] The release of acetylcholine induced by electrical stimulation during rapid atrial pacing plays a major role in overdrive suppression of atrial pacemakers.[26] If the sinus node were hyperresponsive to acetylcholine, rapid atrial pacing might produce a prolonged pause. However, the fact that sinus nodal recovery times were normal in 14 of our 17 patients (82 percent) may invalidate this proposed mechanism. Other suggested explanations for prolonged asystole are an excessive release of acetylcholine or inadequate cholinesterase activity after carotid sinus stimulation.[25]

References

1. **Thomas JE:** Diseases of the carotid sinus—syncope. In Handbook of Clinical Neurology, Vol II, chap 19 (Vinken PJ, Bruyn GW, ed). Amsterdam, North-Holland Publishing, 1972, p 532
2. **Franke H:** Uber das Karotissinus-Syndrom und den sogenannten hyperaktiven Karotissinus-Reflex. Stuttgart, Friedrich-Karl Schattauer-Verlag, 1963, p 149
3. **Thomas JE:** Hyperactive carotid sinus reflex and carotid sinus syncope. Mayo Clin Proc 44:127–139, 1969
4. **Nathanson MH:** Hyperactive cardioinhibitory carotid sinus reflex. Arch Intern Med 77:491–503, 1946

5. **Sigler LH:** The cardioinhibitory carotid sinus reflex. Am J Cardiol 12:175–183, 1963
6. **Scherlag BJ, Lau SH, Helfant RH, et al:** Catheter technique for recording His bundle activity in man. Circulation 39:13–18, 1969
7. **Narula OS, Samet P, Javier RP:** Significance of sinus-node recovery time. Circulation 45:140–158, 1972
8. **Rosen KM, Loeb MS, Sinno MZ, et al:** Cardiac conduction in patients with symptomatic sinus node disease. Circulation. 43: 836–844, 1971
9. **Hutchinson EC, Yates PO:** The cervical portion of the vertebral artery: a clinico-pathological study. Brain 79:319–331, 1956
10. **Peretz DI, Gerein AN, Miyagishima RT:** Permanent demand pacing for hypersensitive carotid sinus syndrome. J Can Med Assoc 108:1131–1134, 1973
11. **Hartzler CO, Maloney JE:** Cardioinhibitory carotid sinus hypersensitivity. Arch Intern Med 137:727–731, 1977
12. **Lown B, Levine SA:** The carotid sinus. Circulation 23:766–789, 1961
13. **Heron JR, Anderson EG, Noble IM:** Cardiac abnormalities associated with carotid-sinus syndrome. Lancet 2:214–216, 1965
14. **Quest JA, Gillis RA:** Effect of digitalis on carotid sinus baroreceptor activity. Circ Res 35:247–255, 1974
15. **Voss DM, Margnin GE:** Demand pacing and carotid sinus syncope. Am Heart J 79:544–547, 1970
16. **Greeley HP, Smedal MI, Most W:** The treatment of the carotid sinus syndrome by irradiation. N Engl J Med 252:91–94, 1955
17. **Cohen FL, Fruehan CT, King RB:** Carotid sinus syndrome. Report of five cases and review of the literature. J Neurosurg 45:78–84, 1976
18. **Gardner RS, Magovern GJ, Park SB, et al:** Carotid sinus syndrome: new surgical considerations. Vasc Surg 9:204–210, 1975
19. **Mandel WJ, Hayakawa H, Allen HN, et al:** Assessment of sinus node function in patients with the sick sinus syndrome. Circulation 46:761–769, 1972
20. **Goldreyer BN:** Sinus node dysfunction—a physiologic consideration of arrhythmias involving the sinus node. Cardiovasc Clin 6: 179–198, 1974
21. **Gupta PK, Lichstein E, Chadda KD, et al:** Appraisal of sinus nodal recovery time in patients with sick sinus syndrome. Am J Cardiol 34:265–270, 1974
22. **Benditt DG, Strauss HC, Scheinman MM, et al:** Analysis of secondary pauses following termination of rapid atrial pacing in man. Circulation 54:436–441, 1976
23. **Scott JC, Reed EA:** Comparison of unilateral with bilateral stimulation of the carotid sinus cardioinhibitory reflex. Am J Physiol 181:27–29, 1955
24. **Reed EA, Scott JC:** Factors influencing the carotid sinus cardioinhibitory reflex. Am J Physiol 181:21–26, 1955
25. **Dighton DH:**Sinus bradycardia. Autonomic influence and clinical assessment. Br Heart J 36:791–797, 1974
26. **Vassale M:** The relationship among cardiac pacemakers. Circ Res 41:269–277, 1977

Initiation of Two Distinct Forms of Atrioventricular Nodal Reentrant Tachycardia During Programmed Ventricular Stimulation in Man

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Of 42 patients with supraventricular tachycardia related to dual atrioventricular (A-V) nodal pathway conduction, 8 had sustained tachycardia induced during programmed ventricular stimulation. The characteristics of the tachycardia in three patients suggested that the A-V nodal reentrant tachycardia used a slow pathway for anterograde conduction and a fast pathway for retrograde conduction (slow-fast form). In these patients, the retrograde effective refractory period was longer in the slow than in the fast pathway. Ventriculoatrial (V-A) conduction curves (V_1-V_2, A_1-A_2) were smooth. Ventricular premature beats, being conducted retrograde over the fast pathway, could activate the slow pathway in an anterograde direction, initiating the slow-fast form of A-V nodal reentrant tachycardia. In the remaining five patients, the tachycardia used a fast pathway for anterograde conduction and a slow pathway for retrograde conduction (fast-slow form). In these patients, the retrograde effective refractory period was longer in the fast than in the slow pathway. V-A conduction curves (V_1-V_2, A_1-A_2) could be either smooth or discontinuous if there was a sudden increase in V-A conduction time. Ventricular premature beats, conducted retrograde over the slow pathway, could activate the fast pathway in an anterograde direction, establishing a tachycardia circuit in reverse of the slow-fast form. In both groups of patients, the ventricular pacing cycle length appeared to be a crucial factor in the ability to expose functional discordance between the two A-V nodal pathways during retrograde conduction.

The fast-slow form of A-V nodal reentrant tachycardia, similar to the slow-fast form, could also be induced during atrial premature stimulation in two patients. In this situation, the slow pathway having an anterograde effective refractory period longer, than that of the fast pathway was a requisite condition; anterograde A-V nodal conduction curves (A_1-A_2, H_1-H_2) were smooth. Atrial premature beats, conducted anterograde over the fast pathway, could activate the slow pathway in a retrograde direction resulting in an atrial echo or sustained fast-slow form of A-V nodal reentrant tachycardia.

Recent electrophysiologic studies[1–14] have suggested that atrioventricular (A-V) nodal reentry, related to the presence of dual A-V nodal pathways, is frequently responsible for the occurrence of paroxysmal supraventricular tachycardia in man. Using the techniques of intracardiac recordings and programmed atrial premature stimulation, most studies describe the induction of an atrial echo or A-V nodal reentrant tachycardia in association with characteristic discontinuous A-V nodal conduction curves (A_1-A_2, H_1-H_2).[3–6,9–14] In contrast, limited information is available concerning the mechanisms of retrograde initiation of A-V nodal reentrant tachycardia during programmed ventricular stimulation in patients with dual A-V nodal pathways.[15–18]

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During the study of eight patients with supraventricular tachycardia, two distinct forms of A-V nodal reentrant tachycardia were elicited during programmed ventricular stimulation; their initiation depended on differences in the electrophysiologic properties of fast and slow A-V nodal pathways during retrograde conduction.

Patients and Methods

Patients: Data of all patients studied in the electrophysiologic laboratories of Jackson Memorial Hospital and the Veterans Administration Hospital, Miami, Florida between July 1974 and June 1977 were reviewed. The following observations suggested the presence of dual A-V nodal pathways: (1) induction of discontinuous A-V nodal conduction curves (A_1-A_2, H_1-H_2) during programmed atrial premature stimulation[3–6,9–14]; or (2) induction of discontinuous ventriculoatrial conduction curves (V_1-V_2, A_1-A_2) during programmed ventricular premature stimulation[16,18–20]; or both (1) and (2). Patients with manifest or concealed accessory A-V bypass tracts[15,21,22] were excluded. Forty-two patients with episodes of supraventricular tachycardia were determined to have dual A-V nodal pathway conduction; in eight of these, sustained (non self-terminating) A-V nodal reentrant tachycardia could be elicited during programmed ventricular stimulation. These eight patients constituted the study population. Their ages ranged from 21 to 64 (mean 38.4) years.

Protocol: After the patients gave informed consent, all cardiotonic and antiarrhythmic medications were discontinued 48 to 72 hours before the study. The study was performed with patients in a postabsorptive nonsedated state. With a conventional technique,[23] the His bundle electrogram was obtained with a tripolar electrode catheter placed across the tricuspid valve, from which low septal right atrial activity was recorded as well. A hexapolar electrode catheter was introduced by way of an antecubital vein. The distal pair of electrodes was placed at the right ventricle for ventricular pacing, and the proximal two pairs were used for high right atrial pacing and recording.[21] The intracardiac electrograms were then displayed simultaneously with standard electrocardiographic leads I, II and V_1 on a multichannel oscilloscopic photographic recorder (Electronics for Medicine, DR-16) and recorded at a paper speed of 100 mm/sec, using a filter setting of 40 to 500 hertz.

Programmed atrial and ventricular stimulation consisted of extrastimulation and incremental pacing.[21] During programmed extrastimulation, the high right atrium and the right ventricular endocardium were respectively stimulated at one or two cycle lengths (A_1-A_1 or V_1-V_1) with use of a programmed digital stimulator (Biocelestronix, Miami Springs, Florida) that delivered stimuli (S_1 and S_2) of 2 msec duration at approximately twice diastolic threshold. After every eighth spontaneous or paced beat (A_1 or V_1), a single premature atrial or ventricular beat (A_2 or V_2) was delivered at progressively shorter coupling intervals (A_1-A_2 or V_1-V_2) until the effective refractory period of the atrium or the ventricle was encountered.[21]

Definitions: A-V conduction intervals and refractory periods were defined and measured as conventionally described.[24] A_1, H_1 and V_1 were low septal right atrial, His bundle and ventricular responses, respectively, induced by the driving stimuli (S_1); A_2, H_2 and V_2 were low septal right atrial, His bundle and ventricular responses, respectively, induced by the premature stimuli (S_2). Ae represented an atrial echo phenomenon or atrial reentry during A-V nodal reentrant tachycardia. The critical A-V nodal conduction time was the A-H interval required for the development of the atrial echo phenomenon or A-V nodal reentrant tachycardia.[3–6,9,13,14] The Ae-H/H-Ae ratio was used to compare anterograde with retrograde A-V nodal conduction time during the episode of A-V nodal reentrant tachycardia. The Ae-H interval was measured from the end of the low septal atrial echo electrogram to the beginning of the His bundle potential and the H-Ae interval from the end of the His bundle potential to the beginning of the low septal atrial echo electrogram.[25]

Electrophysiologic evidence for retrograde conduction over the A-V node–His-Purkinje system was based on the following observations: (1) Progressive prolongation of ventriculoatrial (V-A) conduction time was induced by gradual shortening of the ventricular premature coupling interval (V_1-V_2) and incremental ventricular pacing (V_1-V_1)[21,26,27]; and (2) ventricular premature stimulation during tachycardia did not result in atrial preexcitation.[13,27] When discontinuous A-V nodal conduction curves (A_1-A_2, H_1-H_2) and discontinuous V-A conduction curves (V_1-V_2, A_1-A_2) were respectively induced during anterograde and retrograde conduction studies, the refractory periods of the fast and slow A-V nodal pathways in anterograde and retrograde directions were measured and defined as described by Denes[3] and Wu[16] and their co-workers. Briefly, the curve to the right of the discontinuity reflected the fast A-V nodal pathway conduction, and that to the left represented the slow A-V nodal pathway conduction. In discontinuous A_1-A_2, H_1-H_2 curves, the longest A_1-A_2 interval at which A_2 was blocked in the fast or the slow A-V nodal pathway was defined as the anterograde effective refractory period of the fast or the slow A-V nodal pathway, respectively. Similarly, in discontinuous V_1-V_2, A_1-A_2 curves, the longest V_1-V_2 interval at which V_2 was blocked in the fast or the slow A-V nodal pathway was defined as the retrograde effective refractory period of the fast or the slow A-V nodal pathway, respectively.

Results

The pattern of the tachycardia circuit within the A-V node identified two distinct forms of A-V nodal reentrant tachycardia that could be induced during programmed ventricular stimulation in these eight patients: (1) the slow-fast form using a slow A-V nodal pathway for anterograde conduction and a fast A-V nodal pathway for retrograde conduction (Ae-H/H-Ae ratio greater than 1) (Cases 1 to 3); and (2) the fast-slow form having a tachycardia circuit in reverse of the former using a fast A-V nodal pathway for anterograde conduction and a slow A-V nodal pathway for retrograde conduction (AeH/H-Ae ratio less than 1) (Cases 4 to 8). The anterograde and retrograde A-V conduction patterns in these patients were then analyzed.

Slow-Fast Form of A-V Nodal Reentrant Tachycardia (three patients)

During programmed atrial stimulation, dual A-V nodal pathway conduction was evident in all three patients. In two of these three patients, sustained A-V nodal reentrant tachycardia of the slow-fast form could be elicited after achievement of a critical A-V nodal conduction delay (A-H) during anterograde slow pathway conduction. The same form of A-V nodal reentrant tachycardia could also be elicited with ventricular premature depolarization (V_2) at short premature coupling intervals (V_1-V_2) during programmed ventricular stimulation in these two patients.

As illustrated in Figure 1, both the high right atrium and the right ventricle were driven at a cycle length of 650 msec. The A_1-A_2, H_1-H_2 and A_1-A_2, A_2-H_2 curves were discontinuous because of a sudden increase in A-V nodal conduction time (A_2-H_2) at an atrial premature coupling interval (A_1-A_2) of 460 msec (Fig. 1A). This reflected a failure of anterograde conduction over the fast A-V nodal pathway with resultant slow A-V nodal pathway conduction. The anterograde effective refractory periods of the fast and slow A-V nodal pathways were 460 and 330 msec, respectively. The critical A-H interval that induced an atrial echo phenomenon was 310 msec. Sustained A-V nodal reentrant tachycardia of the slow-fast form could be induced between atrial premature coupling intervals of 360 and 340 msec. The corresponding V_1-V_2, A_1-A_2 and V_1-V_2, V_2-A_2 curves, in contrast, were smooth (Fig. 1B). Note that there was a progressive increase in V-A conduction time (V_2-A_2) as the ventricular premature coupling interval (V_1-V_2) gradually shortened, a characteristic of retrograde conduction

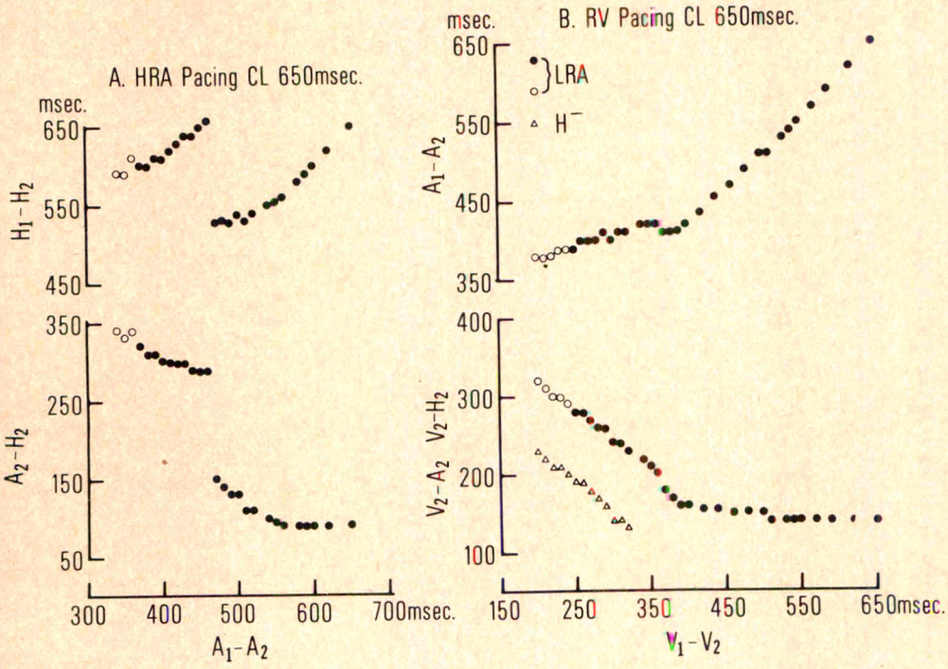

FIGURE 1. Case 1. **A,** A_1-A_2, H_1-H_2 and A_1-A_2, A_2-H_2 curves during high right atrial (HRA) pacing at a cycle length (CL) of 650 msec. Note discontinuity due to a sudden increase in A-V nodal conduction time (A_2-H_2) at a premature coupling interval (A_1-A_2) of 460 msec. **Solid circles** represent responses without atrial echoes; **open circles** represent responses with atrial echoes. (See text.) **B,** V_1-V_2, A_1-A_2 and V_1-V_2, V_2-A_2 curves during right ventricular (RV) pacing at a cycle length (CL) of 650 msec. **Solid circles** represent responses without ventricular echoes; **open circles** represent responses with ventricular echoes. Retrograde His bundle potentials (H^-) are depicted as **open triangles.** Both V_1-V_2, A_1-A_2 and V_1-V_2, V_2-A_2 curves are smooth. Retrograde A-V nodal conduction time (H_2-A_2) ranges from 90 to 100 msec. Induction of sustained A-V nodal reentrant tachycardia of the slow-fast form coincides with the ventricular echo zone between premature coupling intervals (V_1-V_2) of 240 and 220 msec. LRA = low septal right atrium.

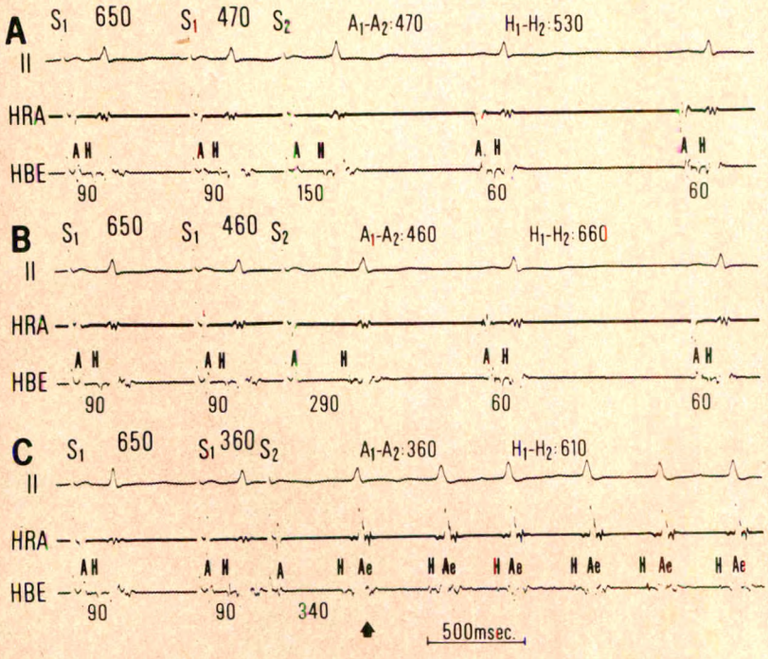

FIGURE 2. Same case. Atrial premature stimulation with induction of the slow-fast form of A-V nodal reentrant tachycardia. In this and subsequent figures are shown electrocardiographic lead II (II), high right atrial (HRA) and His bundle electrographic (HBE) leads. S_1 and S_2 represent pacing and premature stimuli, and A and H atrial and His bundle electrograms, respectively. The high right atrium is driven at a cycle length (S_1-S_1 interval) of 650 msec. **A,** an atrial premature beat at a coupling interval (S_1-S_2) of 470 msec lengthens the A-H interval from 90 to 150 msec. **B,** an atrial premature beat at a coupling interval (S_1-S_2) of 460 msec suddenly prolongs the A-H interval to 290 msec, resulting in discontinuous A-V nodal conduction curves (A_1-A_2, H_1-H_2) (Fig. 1A). **C,** an atrial premature beat at a coupling interval (S_1-S_2) of 360 msec induces a sustained A-V nodal reentrant tachycardia of the slow-fast form upon achievement of an A-H interval of 340 msec **(arrow).** The Ae-H/H-Ae ratio is greater than 1 during tachycardia. Ae = atrial echo phenomenon.

in the A-V node–His-Purkinje system. The retrograde His bundle potential (H_2) secondary to ventricular premature depolarization (V_2) could be recorded between ventricular premature coupling intervals (V_1-V_2) of 320 and 200 msec. Retrograde A-V nodal conduction time (H_2-A_2) ranged from 90 to 100 msec. Because the V-A conduction curve (V_1-V_2, A_1-A_2) was smooth and retrograde A-V nodal conduction time was relatively short, it was concluded that V-A conduction occurred exclusively by way of the fast A-V nodal pathway. Between ventricular premature coupling intervals (V_1-V_2) of 240 and 200 msec, sustained A-V nodal reentrant tachycardia of the slow-fast form, similar to that induced during programmed atrial premature stimulation, could be elicited.

The representative tracings corresponding to Figure 1, A and B, are shown in Figures 2 and 3. Note that the slow-fast form of A-V nodal reentrant tachycardia induced during both atrial and ventricular premature stimulation had an Ae-H/H-Ae ratio of more than 1, indicating anterograde conduction over a slow A-V nodal pathway and retrograde conduction over a fast A-V nodal pathway (Fig. 2C and 3C). Furthermore, shortening of the ventricular pacing cycle length (V_1-V_1) seemed to widen the tachycardia zone. As demonstrated in Figure 3D, when the ventricular pacing cycle length was decreased to 450 msec, a ventricular premature depolarization (V_2) at a relatively long coupling interval (V_1-V_2) of 370 msec could readily elicit a sustained A-V nodal reentrant tachy-

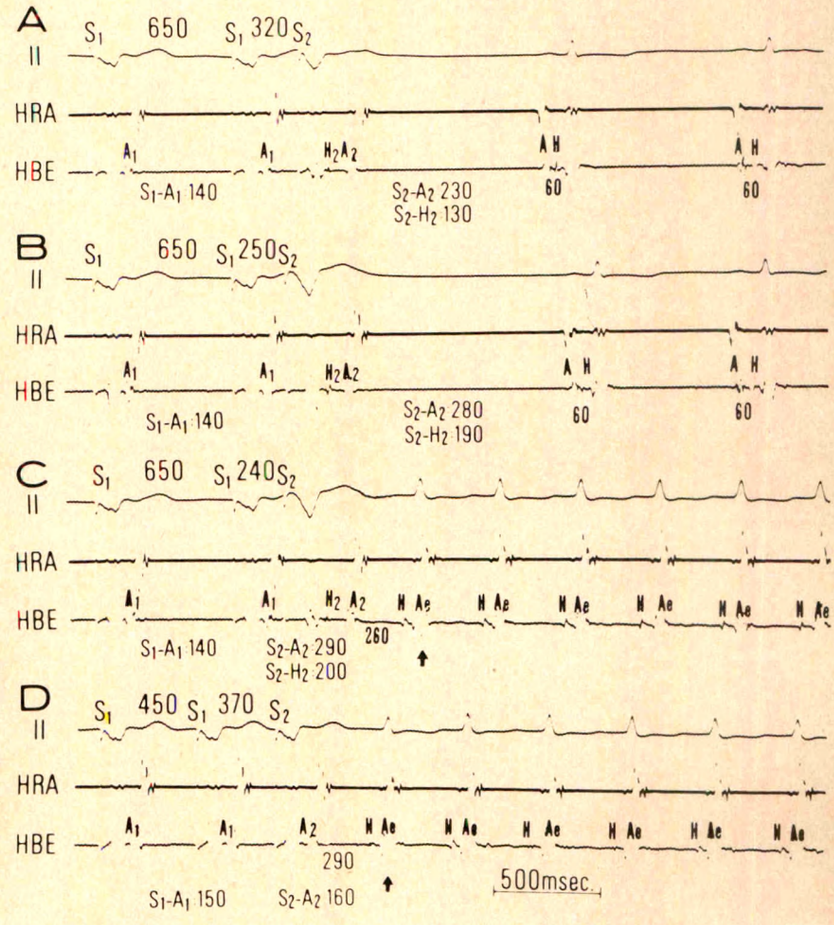

FIGURE 3. Same case. Ventricular premature stimulation with induction of the slow-fast form of A-V nodal reentrant tachycardia. The right ventricle is driven at a cycle length of 650 msec. **A** to **C,** ventricular premature beats (S_2) at coupling intervals of 320, 250 and 240 msec induce retrograde atrial activation with a gradual prolongation of V-A conduction time (S_2-A_2 interval = 230, 280 and 290 msec, respectively). The corresponding V_1-V_2, A_1-A_2 and V_1-V_2, V_2-A_2 curves are smooth (Fig. 1B). Retrograde A-V nodal conduction time (H_2-A_2) is 90 msec. In **C,** the ventricular premature beat (S_2) elicits not only a ventricular echo phenomenon but also sustained A-V nodal reentrant tachycardia of the slow-fast form **(arrow).** The Ae-H/H-Ae ratio is greater than 1 during tachycardia. **D,** when the ventricular pacing cycle length (S_1-S_1) is decreased to 450 msec, a ventricular premature beat (S_2) can induce sustained A-V nodal reentrant tachycardia of the slow-fast form **(arrow)** beginning at a coupling interval (S_1-S_2) of 370 msec until V-A conduction fails at 230 msec (not shown). Abbreviations as in Figure 2.

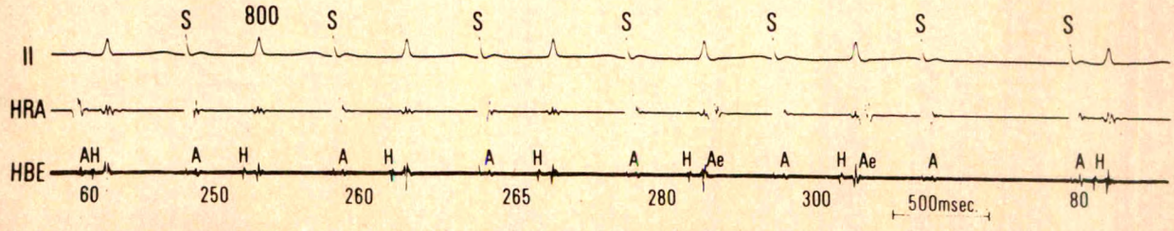

FIGURE 4. Case 2. Anterograde dual A-V nodal pathway conduction during basic atrial pacing. S = stimulus. The first beat is of sinus origin with an A-H interval of 60 msec. The second and subsequent beats are responses to high right atrial pacing at a cycle length of 800 msec. Note a sudden increase in the A-H interval (250 msec) after the first atrial capture. Gradual prolongation of A-V nodal conduction time (A-H) is followed by the occurrence of an atrial echo (Ae) phenomenon (critical A-H interval = 280 msec corresponding to the fourth atrial capture). The sixth atrial capture is blocked in the A-V node. The occurrence of an atrial echo (Ae) phenomenon interferes with programmed atrial premature stimulation. Abbreviations as in Figure 2.

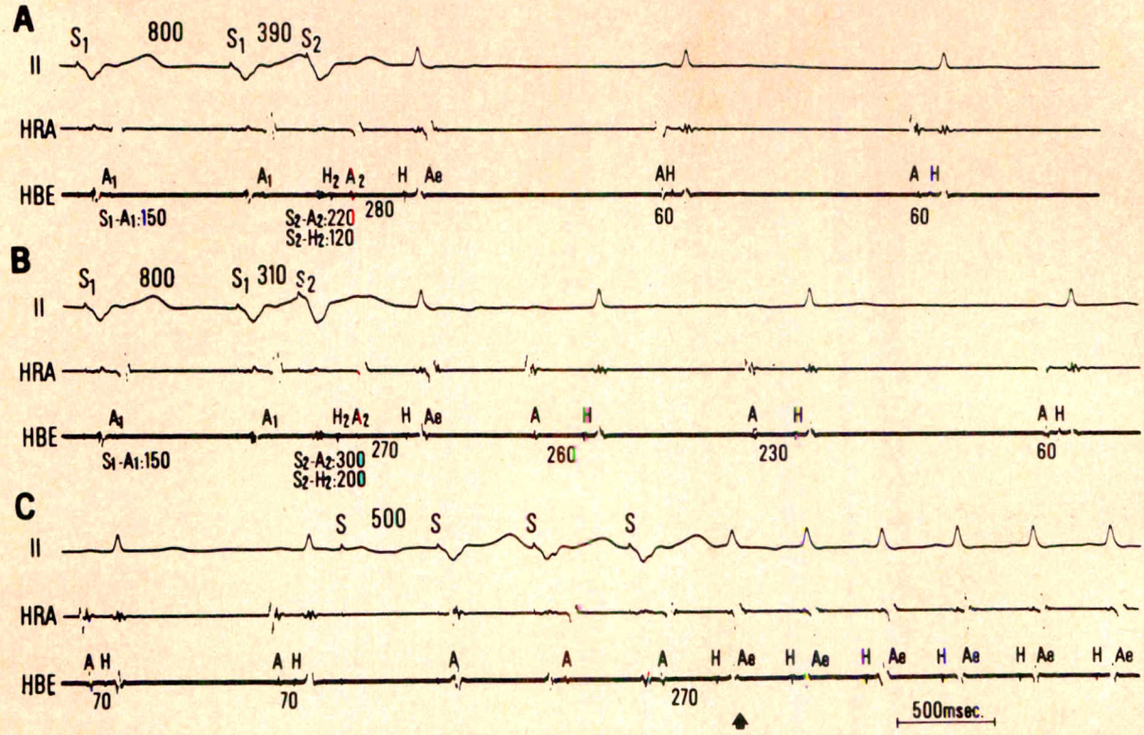

FIGURE 5. Same case. Induction of the slow-fast form of A-V nodal reentrant tachycardia at a shorter ventricular pacing cycle length without ventricular premature stimulation. **A** and **B,** the right ventricle is driven at a cycle length of 800 msec. Ventricular premature beats (S_2) at coupling intervals of 390 and 310 msec induce retrograde atrial activation with a gradual prolongation of V-A conduction time (S_1-A_1 = 150 msec in both panels, S_2-A_2 = 220 and 300 msec, in **A** and **B,** respectively). In each instance, ventriculoatrial activation is followed by a ventricular echo beat with an atrial echo (Ae). The corresponding V_1-V_2, A_1-A_2 and V_1-V_2, V_2-A_2 curves are smooth, similar to those demonstrated in Figure 1B. Retrograde A-V nodal conduction time (H_2-A_2) is 100 msec. **C,** the right ventricular pacing cycle length is decreased from 800 to 500 msec. The third and fourth pacing stimuli not only capture the ventricle but also induce retrograde atrial activation. A sustained A-V nodal reentrant tachycardia of the slow-fast form is elicited after termination of ventricular pacing (the fourth pacing stimulus). The Ae-H/H-Ae ratio is greater than 1 during tachycardia. Abbreviations as in Figure 2.

cardia of the slow-fast form. The tachycardia zone extended from the premature coupling interval (V_1-V_2) of 370 msec to 240 msec before V-A conduction failed (V_1-V_2 interval = 230 msec).

In the remaining patient (Fig. 4), the fast A-V nodal pathway appeared to have a long effective refractory period in an anterograde direction. At an atrial pacing cycle length of 800 msec, anterograde A-V nodal conduction immediately shifted from fast to slow A-V nodal pathway conduction. A gradual prolongation of anterograde conduction time (A-H) over the slow A-V nodal pathway then resulted in retrograde atrial activation (Ae) through the fast A-V nodal pathway interfering with programmed atrial premature stimulation. Neither continuous atrial pacing at various cycle lengths nor rapid atrial stimulation up to 250 beats/min could elicit an episode of A-V nodal reentrant tachycardia. The right ventricle was then driven at a comparable cycle length of 800 msec. V-A conduction time (V_2-A_2) progressively lengthened as the ventricular premature coupling interval (V_1-V_2) gradually shortened, suggesting retrograde conduction over the A-V node–His-Purkinje system (Fig. 5, A to C). Ventricular premature depolarizations (V_2) induced a ventricular echo phenomenon between premature coupling intervals (V_1-V_2) of 390 and 290 msec. Although an atrial echo (Ae) constantly occurred after the ventricular echo beats, no sustained A-V nodal reentrant tachycardia could be elicited. A retrograde His bundle potential (H_2) secondary to ventricular premature depolarization (V_2) was also discernible between premature coupling intervals (V_1-V_2) of 390 and 290 msec. The V-A conduction curve (V_1-V_2, A_1-A_2) was smooth, similar to that illustrated in Figure 1B, and retrograde A-V nodal conduction time (H_2-A_2) was relatively short, ranging from 80 to 100 msec. It was therefore concluded that the fast A-V nodal pathway was used for V-A conduction, and the slow A-V nodal pathway for anterograde conduction during the occurrence of a ventricular echo phenomenon (Fig. 5, A and B). Shortening of the ventricular pacing cycle length to 500 msec could in itself initiate sustained A-V nodal reentrant tachycardia of the slow-fast form (Ae-H/H-Ae greater than 1) without delivery of ventricular premature stimulation (Fig. 5C).

Fast-Slow Form of A-V Nodal Reentrant Tachycardia (five patients)

In two of these five patients, A-V nodal conduction curves (A_1-A_2, H_1-H_2) were smooth during programmed atrial premature stimulation. Nevertheless, atrial premature depolarizations (A_2) at short coupling intervals (A_1-A_2) resulted in the late appearance of an atrial echo (Ae) or sustained A-V nodal reentrant tachycardia of the fast-slow form. During programmed ventricular premature stimulation in these two patients, discontinuous V-A conduction curves (V_1-V_2, A_1-A_2) suggesting retrograde dual A-V nodal pathways were present. However, demonstration of discontinuous V-A conduction curves (V_1-V_2, A_1-A_2) appeared to be dependent on cycle length.

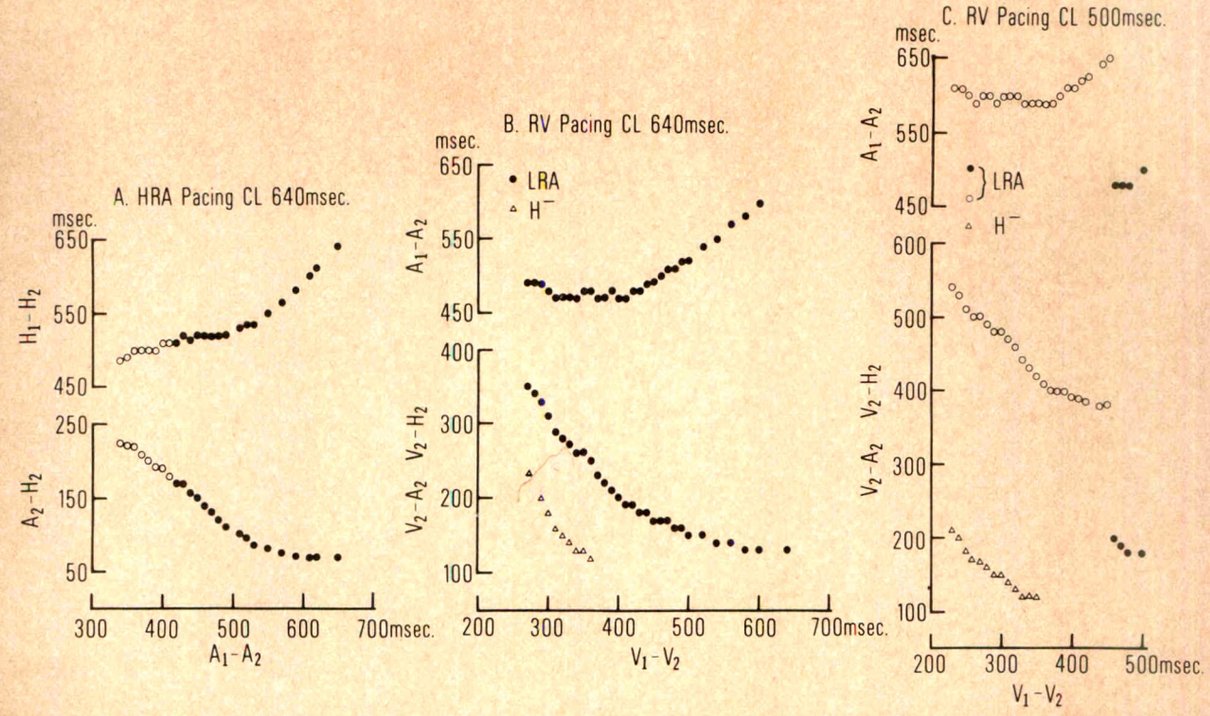

FIGURE 6. Case 4. **A,** A_1-A_2, H_1-H_2 and A_1-A_2, A_2-H_2 curves during high right atrial pacing at a cycle length of 640 msec. **Solid circles** represent responses without atrial echoes, **open circles** represent responses with atrial echoes. Both A_1-A_2, H_1-H_2 and A_1-H_2, A_2-H_2 curves are smooth. A-V nodal conduction time (A_2-H_2) lengthens progressively as the atrial premature coupling interval (A_1-A_2) gradually shortens (see text). **B,** V_1-V_2, A_1-A_2 and V_1-V_2, V_2-A_2 curves during right ventricular pacing at a cycle length of 640 msec. **Solid circles** represent responses without ventricular echoes. Retrograde His bundle potentials (H^-) are depicted as **open triangles.** Both V_1-V_2, A_1-A_2 and V_1-V_2, V_2-A_2 curves are smooth. Retrograde A-V nodal conduction time (V_2-H_2) ranges from 120 to 130 msec. No ventricular echo phenomenon or A-V nodal reentrant tachycardia can be induced. **C,** V_1-V_2, A_1-A_2 and V_1-V_2, V_2-A_2 curves during right ventricular pacing at a cycle length of 500 msec. Note the discontinuity due to a sudden increase in VA conduction time (V_2-A_2) at a ventricular premature coupling interval (V_1-V_2) of 450 msec. **Solid circles** represent responses without ventricular echoes; **open circles** represent responses with ventricular echoes. Retrograde His bundle potentials are depicted as **open triangles.** The curve to the right of discontinuity reflects retrograde fast A-V nodal pathway conduction, that to the left, retrograde slow A-V nodal pathway conduction. Retrograde slow A-V nodal pathway conduction time (H_2-A_2) ranges from 300 to 330 msec. Induction of sustained A-V nodal reentrant tachycardia of the fast-slow form coincides with the entire retrograde slow A-V nodal pathway conduction curve. Abbreviations as in Figure 1.

As illustrated in Figure 6, A and B, both the high right atrium (HRA) and the right ventricle (RV) were driven at a cycle length of 640 msec. The A_1-A_2, H_1-H_2 and A_1-A_2, A_2-H_2 curves were smooth. There was a progressive increase in anterograde A-V nodal conduction time (A-H) as the atrial premature coupling interval (A_1-A_2) gradually shortened (Fig. 6A). The critical A-H interval that induced an atrial echo beat was only 180 msec. Sustained A-V nodal reentrant tachycardia of the fast-slow form could be induced between atrial premature coupling intervals (A_1-A_2) of 350 and 330 msec (Fig. 6A). It was believed that the entire A_1-A_2, H_1-H_2 and A_1-A_2, A_2-H_2 curves reflected the fast A-V nodal pathway conduction, and its anterograde effective refractory period was 320 msec. The slow A-V nodal pathway had an effective refractory period longer than that of the fast A-V nodal pathway in an anterograde direction, and its exact value could not be measured. The corresponding V_1-V_2, A_1-A_2 and V_1-V_2, V_2-A_2 curves were also smooth (Fig. 6B). There was a progressive increase in V-A conduction time (V_2-A_2) as the ventricular premature coupling interval (V_1-V_2) gradually shortened, a characteristic of retrograde conduction in the A-V node–His-Purkinje system. The retrograde His bundle potential (H_2) secondary to ventricular premature depolarization (V_2) could be recorded between premature coupling intervals (V_1-V_2) of 360 and 270 msec. Retrograde A-V nodal conduction time (H_2-A_2) ranged from 120 to 130 msec. Because of the smooth V-A conduction curve (V_1-V_2, A_1-A_2) and relatively short retrograde A-V nodal conduction time (H_2-A_2), it was concluded that the fast A-V nodal pathway was used exclusively for retrograde atrial activation during programmed ventricular premature stimulation at this selected pacing cycle length.

The ventricular pacing cycle length was then decreased from 640 to 500 msec in the same patient (Fig. 6C). At this pacing cycle length, a sudden increase in V-A conduction time (V_2-A_2) occurred between premature coupling intervals of 460 and 450 msec resulting in discontinuous V-A conduction curves (V_1-V_2, A_1-A_2). This indicated a failure of retrograde conduction over the fast A-V nodal pathway with resultant slow A-V nodal pathway conduction. The curve to the right of discontinuity reflected retrograde fast A-V nodal pathway conduction and to the left, retrograde slow A-V nodal pathway conduction. The retrograde effective refractory period of the fast A-V nodal pathway was 450 msec and that of the slow A-V nodal pathway 220 msec. V-A conduction time (V_2-A_2) of both the retrograde fast and slow A-V nodal pathway conduction curves showed characteristic progressive lengthening as the ventricular premature coupling interval (V_1-V_2) gradually shortened (Fig. 6C). The retrograde His bundle potential (H_2) secondary to ventricular premature depolarization (V_2) could be recorded between premature coupling intervals (V_1-V_2) of 350 and 230 msec. Retrograde A-V nodal conduction time (H_2-A_2) was relatively long (300 to 330 msec), thus confirming that the slow A-V nodal pathway was used for retrograde atrial

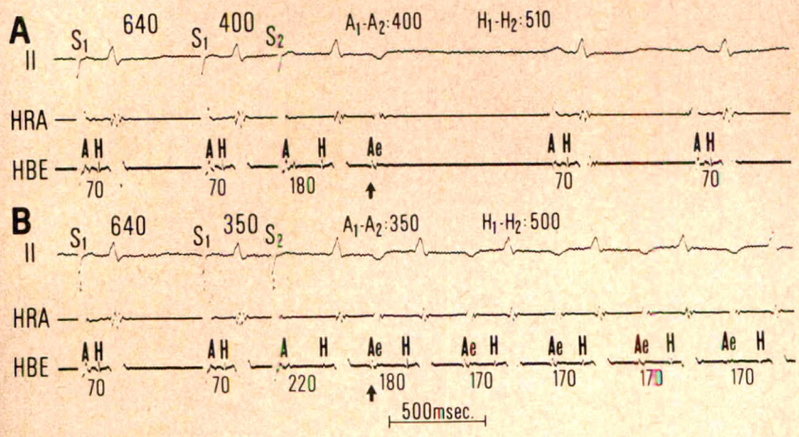

FIGURE 7. Same case. Atrial premature stimulation with induction of the fast-slow form of A-V nodal reentrant tachycardia. The high right atrium is driven at a cycle length (S_1-S_1) of 640 msec. The A-V nodal conduction time (A-H) lengthens progressively as the atrial premature coupling interval (S_1-S_2) gradually shortens. The corresponding A_1-A_2, H_1-H_2 and A_1-A_2, A_2-H_2 curves are smooth (Fig. 6A). **A,** an atrial premature beat at a coupling interval (S_1-S_2) of 400 msec lengthens the A-H interval from 70 to 180 msec and elicits the late appearance of an atrial echo (Ae) **(arrow).** Note that the anterograde/retrograde A-V nodal conduction time ratio (A-H = 130 msec/H-Ae = 250 msec) is less than 1. **B,** an atrial premature beat at a coupling interval of 350 msec elicits not only an atrial echo (Ae) phenomenon but also a sustained fast-slow form of A-V nodal reentrant tachycardia **(arrow).** The Ae/H/H-Ae ratio is less than 1 during tachycardia, indicating anterograde conduction over a fast A-V nodal pathway and retrograde conduction over a slow A-V nodal pathway. Abbreviations as in Figure 2.

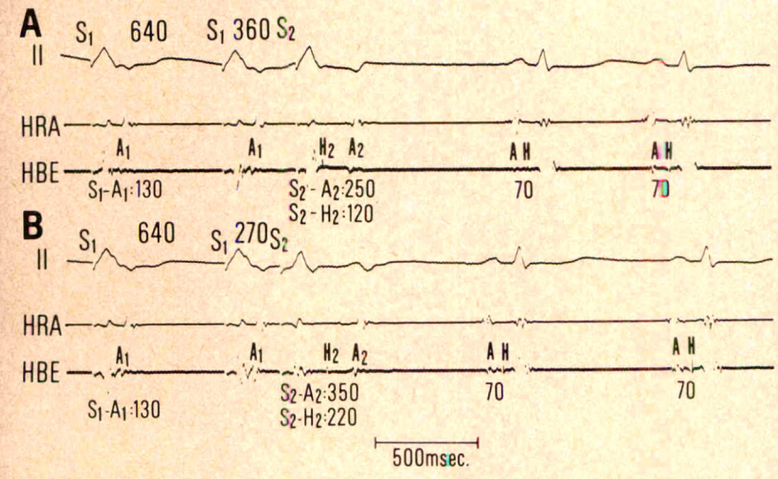

FIGURE 8. Same case. Ventricular premature stimulation without induction of A-V nodal reentrant tachycardia of either form. The right ventricle is driven at a cycle length (S_1-S_2) of 640 msec. **A** and **B,** ventricular premature beats (S_2) at coupling intervals (S_1-S_2) of 360 msec and 270 msec progressively lengthen V-A conduction time (S_1-A_1 = 130, S_2-A_2 = 250 and 350 msec, respectively) without induction of a ventricular echo phenomenon or A-V nodal reentrant tachycardia. Retrograde A-V nodal conduction time (H_2-A_2) is 130 msec. Abbreviations as in Figure 2.

activation after the sudden increase in V-A conduction time (V_2-A_2). Throughout the entire retrograde slow A-V nodal pathway conduction curve (V_1-V_2, A_1-A_2), a ventricular premature depolarization (V_2) could elicit not only a ventricular echo phenomenon but also sustained A-V nodal reentrant tachycardia of the fast-slow form.

The representative tracings corresponding to Figure 6, A to C, are shown in Figures 7, 8 and 9. Note that the fast-slow form of A-V nodal reentrant tachycardia induced during both atrial and ventricular premature stimulation had an Ae-H/H-Ae ratio of less than 1, indicating anterograde conduction over a fast A-V nodal pathway and retrograde conduction over a slow A-V nodal pathway (Fig. 7B and 9, B to D).

In the other three patients, discontinuous A-V nodal conduction curves (A_1-A_2, H_1-H_2) suggestive of the presence of dual A-V nodal pathways were evident during programmed atrial premature stimulation. However, no atrial echo phenomenon or A-V nodal reentrant tachycardia of either form could be elicited. During programmed ventricular stimulation, two of the three patients had discontinuous V-A conduction curves (V_1-V_2, A_1-A_2) suggesting dual A-V nodal pathways in the retrograde direction. Sustained A-V nodal reentrant tachycardia of the fast-slow form could be induced after a shift from retrograde fast to retrograde slow A-V nodal pathway conduction, similar to that illustrated in Figures 6C and 9, A to D. In the remaining patient, a prolonged V-A conduction time (V_1-A_1) before ventricular premature stimulation suggested retrograde conduction over a slow A-V nodal pathway. Induction of the fast-slow form of A-V nodal reentrant tachycardia by ventricular premature beats (V_2) was associated with a smooth V-A conduction curve (V_1-V_2, A_1-A_2).

As illustrated in Figure 10, both the high right atrium and the right ventricle were driven at a cycle length of 650 msec. The A_1-A_2, H_1-H_2 and A_1-A_2, A_2-H_2 curves were discontinuous because of a sudden increase in A-V nodal conduction time (A_2-H_2) at an atrial premature coupling interval (A_1-A_2) of 340 msec (Fig. 10A). This reflected a failure of anterograde conduction over the fast A-V nodal pathway with resultant slow A-V nodal pathway conduction. The anterograde effective refractory period of the fast A-V nodal pathway was 340 msec. A further decrease in the atrial premature coupling interval (A_1-A_2) did not induce an atrial echo phenomenon or A-V

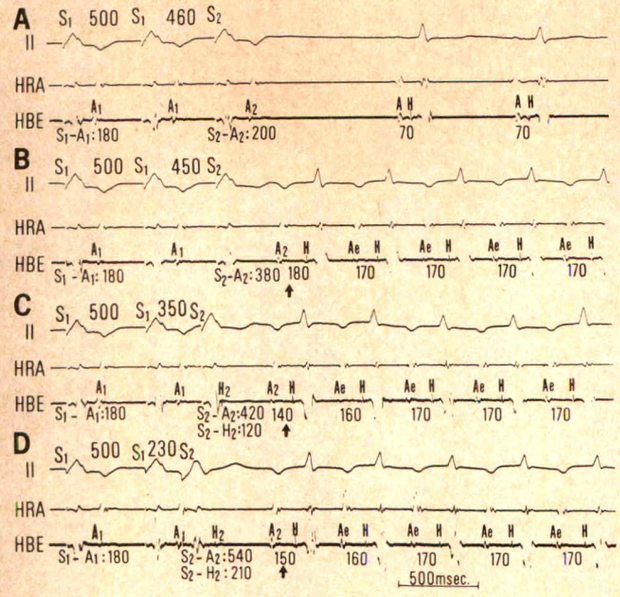

FIGURE 9. Same case. Ventricular premature stimulation with induction of the fast-slow form of A-V nodal reentrant tachycardia. The right ventricle is driven at a cycle length (S_1-S_1) of 500 msec. **A,** a ventricular premature beat (S_2) at a coupling interval (S_1-S_2) of 460 msec lengthens V-A conduction time (S_2-A_2) from 180 to 200 msec. **B,** a ventricular premature beat (S_2) at a coupling interval (S_1-S_2) of 450 msec suddenly increases V-A conduction to 380 msec, resulting in discontinuous V-A conduction curves (V_1-V_2, A_1-A_2) (Fig. 6C) and induction of a sustained A-V nodal reentrant tachycardia of the fast-slow form **(arrow). C** and **D,** ventricular premature beats (S_2) at coupling intervals (S_1-S_2) of 350 and 230 msec further progressively lengthen V-A conduction time (S_2-A_2) to 420 and 540 msec, respectively, and induce sustained A-V nodal reentrant tachycardia of the fast-slow form **(arrow).** Retrograde A-V nodal conduction time (H_2-A_2) is 300 and 330 msec, respectively. Note the Ae-H/H-Ae ratio is less than 1 during tachycardia. Abbreviations as in Figure 2.

nodal reentrant tachycardia. The determination of the anterograde effective refractory period of the slow A-V nodal pathway was limited by atrial refractoriness. Premature atrial stimulation at a shorter atrial pacing cycle length of 450 msec and rapid atrial stimulation up to 250 beats/min also failed to elicit an atrial echo phenomenon or A-V nodal reentrant tachycardia. In contrast, the corresponding V_1-V_2, A_1-A_2 and V_1-V_2, V_2-A_2 curves were smooth (Fig. 10B). Note the relatively long V-A conduction time during basic ventricular driving (V_1-A_1 = 310 msec) and the progressive increase in V-A conduction time (V_2-A_2) as the ventricular premature coupling interval (V_1-V_2) gradually shortened, characteristic of retrograde conduction by way of the A-V node–His-Purkinje system.

The retrograde His bundle potential (H_2) secondary to ventricular premature depolarization (V_2) could be recorded between ventricular premature coupling intervals (V_1-V_2) of 310 and 290 msec. Retrograde A-V nodal conduction time (H_2-A_2) ranged from 270 to 280 msec. Because of the smooth V-A conduction curve (V_1-V_2, A_1-A_2) and relatively long retrograde A-V nodal conduction time, it was concluded that the slow A-V nodal pathway was used exclusively for V-A conduction. The retrograde effective refractory period of the slow A-V nodal pathway was 280 msec. The fast A-V nodal pathway had a retrograde effective refractory period longer than that of the slow A-V nodal pathway and its exact value could not be measured. Between ventricular premature coupling intervals (V_1-V_2) of 470 to 290 msec, ventricular premature depolarizations (V_2) constantly elicited sustained A-V nodal reentrant tachycardia of the fast-slow form.

The representative tracings corresponding to Figure 10, A and B, are shown in Figures 11 and 12. Note that the A-V nodal reentrant tachycardia induced during ventricular premature stimulation had an Ae-H/H-Ae ratio of less than 1, indicating anterograde conduction over a fast A-V nodal pathway and retrograde conduction over a slow A-V nodal pathway (Fig. 12, A to C).

The fast-slow form of A-V nodal reentrant tachycardia could also be triggered by a decrease in the ven-

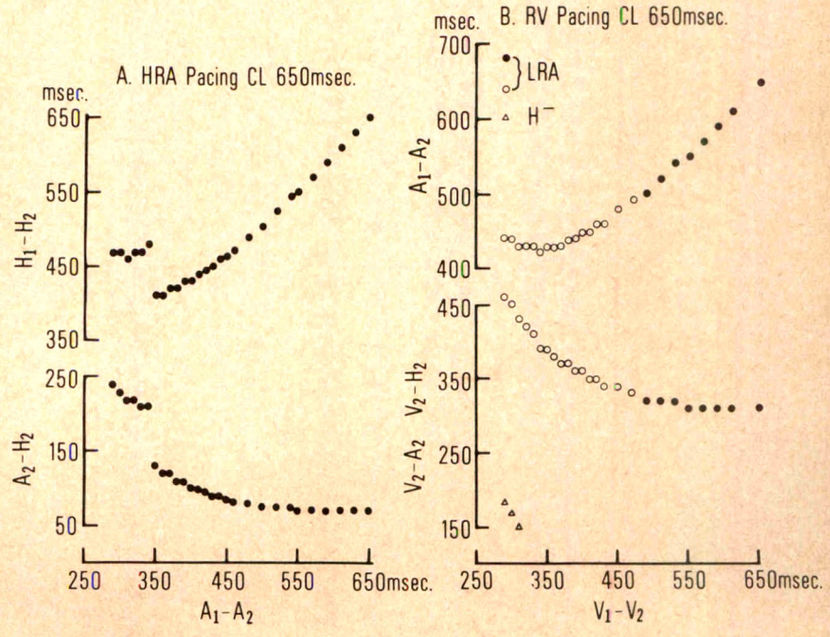

FIGURE 10. Case 6. **A,** A_1-A_2, H_1-H_2 and A_1-A_2, A_2-H_2 curves during high right atrial pacing at a cycle length of 650 msec. Note discontinuity due to a sudden increase in A-V nodal conduction time (A_2-H_2) at a premature coupling interval of 340 msec. **Solid circles** represent responses without atrial echoes. No atrial echo phenomenon or A-V nodal reentrant tachycardia can be induced (see text). **B,** V_1-V_2, A_1-A_2 and V_1-V_2, V_2-A_2 curves during right ventricular pacing at a cycle length of 650 msec. **Solid circles** represent responses without ventricular echoes; **open circles** represent responses with ventricular echoes. Retrograde His bundle potentials (H^-) are depicted as **open triangles.** Both V_1-V_2, A_1-A_2 and V_1-V_2, V_2-A_2 curves are smooth. Note the relatively long V-A conduction time during basic driving (V_1-A_1 = 310 msec). Retrograde A-V nodal conduction time (H_2-A_2) ranges from 270 to 280 msec. Induction of sustained A-V nodal reentrant tachycardia of the fast-slow form coincides with the entire ventricular echo zone between premature coupling intervals (V_1-V_2) of 470 and 290 msec. Abbreviations as in Figure 1.

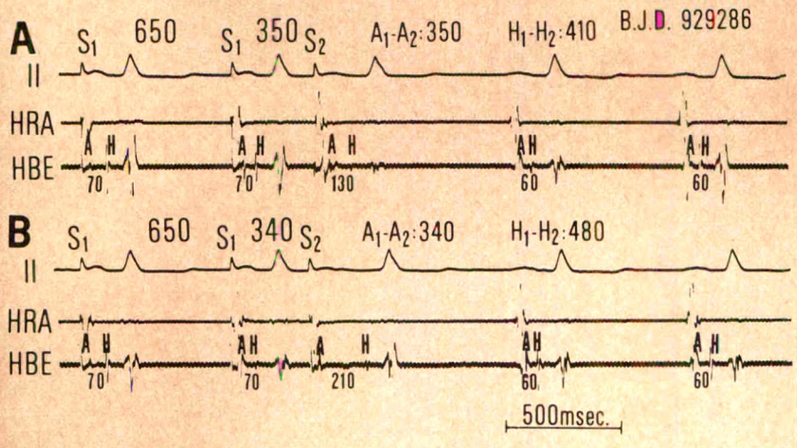

FIGURE 11. Same patient. Atrial premature stimulation without induction of A-V nodal reentrant tachycardia of either form. The high right atrium was driven at a cycle length (S_1-S_1) of 650 msec. **A,** an atrial premature beat at a coupling interval (S_1-S_2) of 350 msec lengthens the A-H interval from 70 to 130 msec. **B,** an atrial premature beat at a coupling interval (S_1-S_2) of 340 msec suddenly increases the A-H interval to 210 msec, resulting in discontinuous A-V nodal conduction curves (A_1-A_2, H_1-H_2) (Fig. 10A). No atrial echo phenomenon or A-V nodal reentrant tachycardia can be induced by further shortening of the atrial premature coupling interval (S_1-S_2). Abbreviations as in Figure 2.

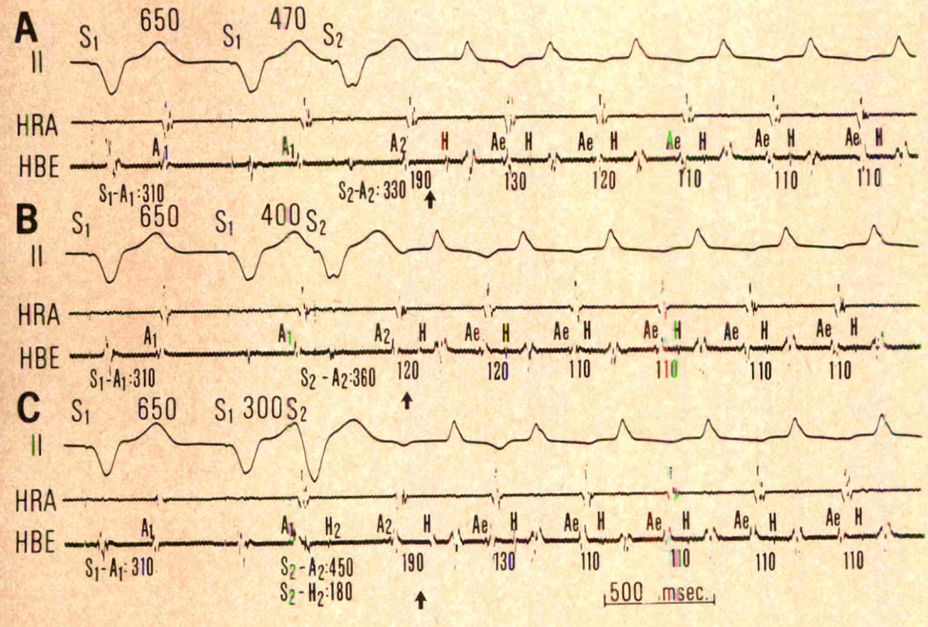

FIGURE 12. Same case. Ventricular premature stimulation with induction of the fast-slow form of A-V nodal reentrant tachycardia. The right ventricle is driven at a cycle length of 650 msec. V-A conduction time is relatively long during basic driving (V_1-A_1 = 310 msec). **A** to **C,** ventricular premature beats (S_2) at coupling intervals of 470, 400 and 300 msec induce retrograde atrial activation with a progressive prolongation of V-A conduction time (S_2-A_2 = 330, 360 and 450 msec, respectively). The corresponding V_1-V_2, A_1-A_2 and V_1-V_2, V_2-A_2 curves are smooth (Fig. 10B). In each instance, retrograde atrial activation is followed by development of a ventricular echo phenomenon and induction of sustained A-V nodal reentrant tachycardia of the fast-slow form **(arrow).** Retrograde A-V nodal conduction time (H_2-A_2) is 270 msec (**C**). The Ae-H/H-Ae ratio is less than 1 during tachycardia. Abbreviations as in Figure 2.

tricular pacing cycle length in three of the five patients. Two examples are shown in Figure 13, A and B. This response indicated that cycle length shortening, possibly by facilitating retrograde block in the fast A-V nodal pathway and prolonging retrograde conduction time in the slow A-V nodal pathway, favored the initiation of the fast-slow form of A-V nodal reentrant tachycardia in these patients.

Discussion

Dual A-V nodal pathway conduction: Both animal and human experiments have demonstrated that the A-V node can undergo functional longitudinal dissociation into two conducting pathways differing in electrophysiologic properties.[3–6,9–14,19,28–31] These two A-V nodal pathways converge proximally as well as distally to form proximal and distal common pathways. An atrial or ventricular premature impulse may thus induce a reentry mechanism utilizing one pathway for anterograde conduction and the other pathway for retrograde conduction, or vice versa, with initiation of an atrial or ventricular echo phenomenon or sustained A-V nodal reentrant tachycardia.

Induction of sustained A-V nodal reentrant tachycardia during programmed ventricular stimulation has rarely been observed in man.[15,16,18] It occurred in 8 of our 42 patients with paroxysmal supraventricular tachycardia associated with dual A-V nodal pathway conduction. Two distinct forms of A-V nodal reentrant tachycardia could be clearly differentiated—the slow-fast form using a slow A-V nodal pathway for anterograde conduction and a fast A-V nodal pathway for retrograde conduction (Ae-H/H-Ae > 1), and the fast-slow form with a tachycardia circuit of the reversed direction (Ae-H/H-Ae $\leq$ 1). In this study we demonstrated that both forms of A-V nodal reentrant tachycardia can be elicited from the atria as well as from the ventricles.

The fast-slow form of A-V nodal reentrant tachycardia frequently presents as a "permanent" form of

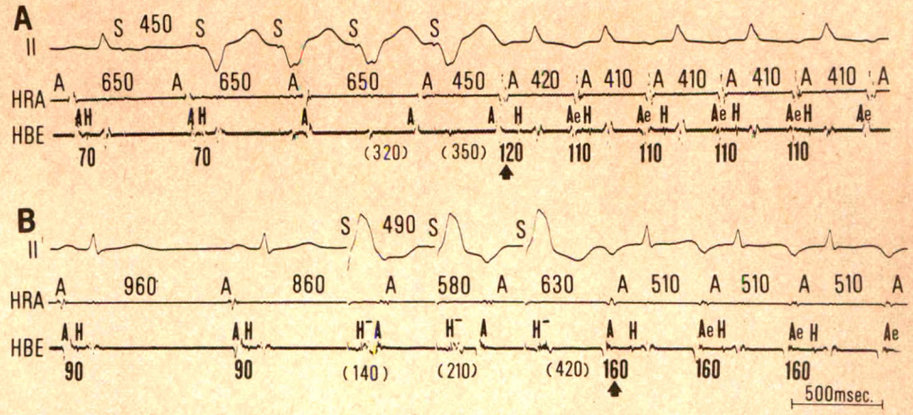

FIGURE 13. Same case. Induction of the fast-slow form of A-V nodal reentrant tachycardia with ventricular pacing at shorter cycle lengths without delivery of ventricular premature stimulation. S represents the ventricular pacing stimulus. **A,** the right ventricle is driven at a cycle of 450 msec. The fourth and fifth pacing stimuli not only capture the ventricle but also induce V-A conduction with a relatively long V-A conduction time (320 msec and 350 msec, respectively [in parentheses]), suggesting retrograde conduction over a slow A-V nodal pathway. After the fifth pacing stimulus, a sustained A-V nodal reentrant tachycardia of the fast-slow form is initiated **(arrow).** The Ae-H/H-Ae is less than 1 during tachycardia. **B,** the right ventricle is driven at a cycle length of 490 msec. H^- indicates retrograde His bundle potentials. The three pacing stimuli all capture the ventricle and induce V-A conduction. There is an atypical Wenckebach periodicity of the V-A conduction time (140, 210 and 420 msec, respectively [in parentheses]), followed by development of a sustained A-V nodal reentrant tachycardia of the fast-slow form **(arrow).** The Ae-H/H-Ae ratio is less than 1 during tachycardia. The sudden increase in V-A conduction time corresponding to the third ventricular captured beat is believed to be due to a failure of retrograde conduction over the fast A-V nodal pathway (retrograde unidirectional block) with resultant conduction over the slow A-V nodal pathway.

supraventricular tachycardia.[7] It resembles, electrocardiographically, an ectopic atrial tachycardia and probably occurs more commonly in children than in adults.[7] Using the technique of atrial and ventricular premature stimulation, Coumel et al.[7,32] postulated A-V nodal reentry as the underlying mechanism. Of note, Satake et al.[20] could demonstrate the occurrence of both anterograde and retrograde dual A-V nodal pathway conduction in the same patient, and Wu et al.[16] documented the association of sustained A-V nodal reentrant tachycardia of this form with discontinuous V-A conduction curves (V_1-V_2, A_1-A_2).

During programmed atrial premature stimulation, recording of the His bundle potential illustrated that a sudden increase in A-V nodal conduction time (A-H) is the cause of discontinuity in the anterograde A-V conduction pattern. This suggested that failure of an anterograde fast A-V nodal pathway is followed by conduction by way of an anterograde slow A-V nodal pathway.[3–6,9–14] However, during programmed ventricular premature stimulation, delineation of the exact routes of V-A conduction is frequently handicapped by the difficulty and uncertainty in recording a retrograde His bundle potential.[21,26,27] In our laboratories, we routinely identify His bundle deflections of sinus beats after delivery of each ventricular premature stimulation and, accordingly, adjust the position of the recording electrode catheter whenever it is necessary. Registration of the retrograde His bundle potential at short ventricular premature coupling intervals[33,34] in these eight patients was of value in helping to delineate which A-V nodal pathway was utilized for V-A conduction and, more importantly, provided significant information pertaining to the understanding of the mechanisms of ventricular echo phenomenon and retrograde initiation of A-V nodal reentrant tachycardia in man.

A-V nodal reentrant tachycardia initiated during programmed atrial premature stimulation: The slow-fast form of A-V nodal reentrant tachycardia may be elicited by an atrial premature beat if the fast A-V nodal pathway has an anterograde effective refractory period longer than that of the slow A-V nodal pathway. Its occurrence is associated with discontinuous anterograde A-V nodal conduction curves (A_1-A_2, H_1-H_2) and requires achievement of a critical A-V nodal conduction delay (A-H) with failure of anterograde conduction by way of the fast A-V nodal pathway and resultant conduction by way of the slow A-V nodal pathway (Fig. 14A).[3–6,9–14] On the other hand, initiation of the fast-slow form of A-V nodal reentrant tachycardia during atrial premature stimulation is only possible when the slow A-V nodal pathway has an anterograde effective refractory period longer than that of the fast A-V nodal pathway. In this situation, the anterograde effective refractory period of the slow A-V nodal pathway cannot be measured, and all the atrial impulses will be exclusively conducted over the fast A-V nodal pathway in the anterograde direction, thus producing a smooth A-V nodal conduction curve (A_1-A_2, H_1-H_2). The critical A-V nodal conduction delay (A-H) required for induction of an atrial echo phenomenon or A-V nodal reentrant tachycardia, or both, may be only minimal because it will be within the range of anterograde conduction time of the fast A-V nodal pathway (Fig. 14B).

Ventricular echo phenomenon and A-V nodal reentrant tachycardia initiated during programmed ventricular stimulation: In addition to the proposed mechanism of intraventricular reentry involving the His-Purkinje system,[35,36] a ventricular echo phenomenon may occur as a result of delayed retrograde conduction of a ventricular premature depolarization within the A-V node.[19,28–31] The presence of dual A-V

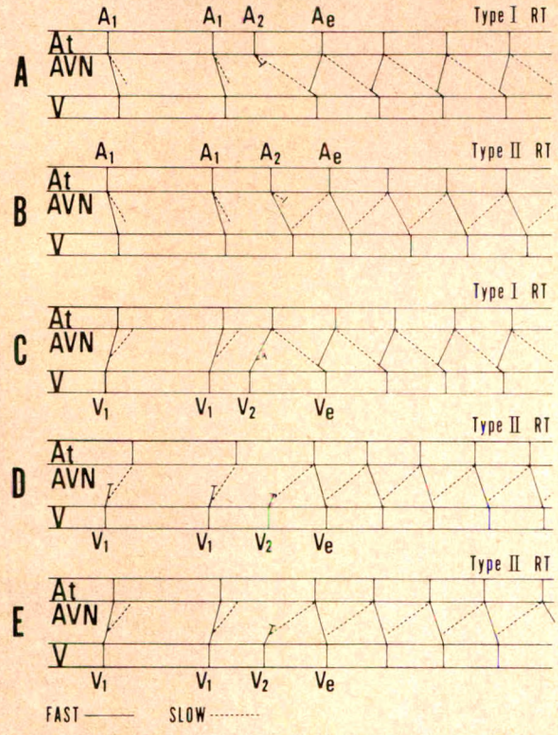

FIGURE 14. Diagrammatic representation of induction of two different forms of A-V nodal reentrant tachycardia (RT) during programmed atrial (**A** and **B**) and ventricular (**C, D** and **E**) premature stimulation. **A, B, C, D** and **E** correspond to Figures 2C, 7B, 3C, 12A and 9B, respectively (see text). At = atrium; AVN = A-V node; V = ventricle. A_1 and V_1 are basic atrial and ventricular drives, respectively. A_2 and V_2 are atrial and ventricular premature complexes, respectively. Ae and Ve represent atrial and ventricular echoes, respectively. Type I and Type II RT = the slow-fast and fast-slow form, respectively, of A-V nodal reentrant tachycardia.

nodal pathways differing in electrophysiologic properties in a retrograde direction favors the occurrence of the ventricular echo phenomenon.

If the slow A-V nodal pathway has a retrograde effective refractory period longer than that of the fast A-V nodal pathway, V-A conduction proceeds exclusively over the fast A-V nodal pathway during programmed ventricular premature stimulation, producing a smooth V-A conduction curve (V_1-V_2, A_1-A_2). At critical premature coupling intervals, a ventricular premature beat, being blocked retrograde in the slow A-V nodal pathway, is conducted over the fast A-V nodal pathway in the retrograde direction and may, in turn, activate the slow A-V nodal pathway in the anterograde direction, resulting in a ventricular echo beat. This ventricular echo phenomenon, when perpetuated, leads to the slow-fast form of A-V nodal reentrant tachycardia, using the fast A-V nodal pathway for retrograde conduction and the slow A-V nodal pathway for anterograde conduction (Fig. 14C).

If the slow A-V nodal pathway has a retrograde effective refractory period shorter than that of the fast A-V nodal pathway, V-A conduction proceeds either exclusively over the slow A-V nodal pathway or over the fast A-V nodal pathway at long premature coupling intervals but over the slow A-V nodal pathway at short premature coupling intervals. In the former situation, exclusive V-A conduction over the slow A-V nodal pathway produces a smooth V-A conduction curve (V_1-V_2, A_1-A_2). In the latter situation, failure of retrograde propagation over the fast A-V nodal pathway followed by a shift in conduction in a retrograde direction over the slow A-V nodal pathway results in a sudden increase in V-A conduction time and, subsequently, discontinuous V-A conduction curves (V_1-V_2, A_1-A_2). In both situations, a ventricular premature beat, being blocked retrograde in the fast A-V nodal pathway, is conducted over the slow A-V nodal pathway in a retrograde direction, and may, in turn activate the fast A-V nodal pathway in an anterograde direction, resulting in a ventricular echo beat. This ventricular echo phenomenon, when perpetuated, leads to the fast-slow form of A-V nodal reentrant tachycardia using the slow A-V nodal pathway for retrograde conduction and the fast A-V nodal pathway for anterograde conduction (Fig. 14, D and E).

A decrease in the ventricular pacing cycle length seems to facilitate initiation of either type of A-V nodal reentrant tachycardia. This is because a shorter ventricular pacing cycle length tends to prolong retrograde conduction time in one A-V nodal pathway and may simultaneously lengthen the retrograde effective refractory period in the other A-V nodal pathway (development of retrograde unidirectional block).[37] Widening of the ventricular echo zone or self-induction (requiring no ventricular premature stimulation) of A-V nodal reentrant tachycardia of either form may thus be observed at shorter ventricular pacing cycle lengths (Fig. 3D, 5C and 13, A and B).

Electrocardiographic differentiation: In the slow-fast form of A-V nodal reentrant tachycardia, the retrograde P wave usually coincides with the QRS complex, hardly discernible from the surface electrocardiogram.[15,38] This is because the retrograde fast A-V nodal pathway is used for retrograde atrial activation at a time when the impulse is also being transmitted in an anterograde direction to the ventricles. In contrast, when the slow A-V nodal pathway is used for retrograde atrial activation, as in the fast-slow form of A-V nodal reentrant tachycardia, the retrograde P wave is inscribed far behind the QRS complex. Differential diagnosis between the fast-slow form of A-V nodal reentrant tachycardia and reciprocating tachycardia using the A-V node–His-Purkinje system for anterograde conduction and a concealed accessory A-V bypass tract for retrograde conduction (concealed Wolff-Parkinson-White syndrome) then becomes necessary because the retrograde P wave in the latter situation is also inscribed after the QRS complex. Our previous[22] and current observations indicate that the fast-slow form of A-V nodal reentrant tachycardia has an R-P interval longer than that of the P-R interval, whereas in reciprocating tachycardia related to a concealed accessory A-V bypass tract, the R-P interval is shorter than the P-R interval. Long and short R-P intervals during the

tachycardia, under these circumstances, reflect retrograde atrial activation through a slow A-V nodal pathway and a fast conducting A-V bypass tract, respectively. However, cardiotonic or antiarrhythmic medications, such as digitalis, propranolol, quinidine or procainamide, and physiologic alterations, such as hypoxia and ischemic processes, may influence the conduction properties of both the A-V node and the accessory bypass tract. Consequently, the characteristics described for each type of tachycardia may be obscured. Electrophysiologic study with intracardiac recordings may be necessary for delineating the underlying mechanisms in certain patients.

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References

1. **Bigger JT Jr, Goldreyer BN:** The mechanism of supraventricular tachycardia. Circulation 42:673–688, 1970
2. **Goldreyer BN, Bigger JT Jr:** Site of reentry in paroxysmal supraventricular tachycardia in man. Circulation 43:15–26, 1971
3. **Denes P, Wu D, Dhingra RC, et al:** Demonstration of dual A-V nodal pathways in patients with paroxysmal supraventricular tachycardia. Circulation 48:549–555, 1973
4. **Wu D, Denes P, Dhingra RC, et al:** The effects of propranolol on induction of A-V nodal reentrant paroxysmal tachycardia. Circulation 50:665–677, 1974
5. **Wu D, Wyndam CRC, Amat-y-Leon R, et al:** The effects of ouabain on induction of atrioventricular nodal reentrant paroxysmal supraventricular tachycardia. Circulation 52:201–207, 1975
6. **Denes P, Wu D, Dhingra RC, et al:** Dual atrioventricular nodal pathways. A common electrophysiological response. Br Heart J 37:1069–1076, 1975
7. **Coumel P:** Junctional reciprocating tachycardias. The permanent and paroxysmal forms of A-V nodal reciprocating tachycardias. J Electrocardiol 8:79–90, 1975
8. **Wellens HJJ, Duren DR, Liem KL, et al:** Effect of digitalis in patients with paroxysmal atrioventricular nodal tachycardia. Circulation 52:779–788, 1975
9. **Wu D, Denes P:** Mechanisms of paroxysmal supraventricular tachycardia. Arch Intern Med 135:437–442, 1975
10. **Neuss H, Schlepper M, Spies HF:** Effects of heart rate and atropine on "dual A-V conduction". Br Heart J 37: 1216–1227, 1975
11. **Touboul P, Huerta F, Porte J, et al:** Reciprocal rhythm in patients with normal electrocardiogram: evidence for dual conduction pathways. Am Heart J 91:3–10, 1976
12. **Bisset JK, de Soyza N, Kane JJ, et al:** Atrioventricular conduction patterns in patients with paroxysmal supraventricular tachycardia. Am Heart J 91:287–291, 1976
13. **Barold SS, Coumel P:** Mechanisms of atrioventricular junctional tachycardia. Role of reentry and concealed accessory bypass tracts. Am J Cardiol 39:97–106, 1977
14. **Josephson ME, Kastor JA:** Supraventricular tachycardia: mechanisms and management. Ann Intern Med 87:346–354, 1977
15. **Wellens HJJ, Durrer D:** The role of an accessory atrioventricular pathway in reciprocal tachycardia. Observations in patients with and without the Wolff-Parkinson-White syndrome. Circulation 52:58–72, 1975
16. **Wu D, Denes P, Amat-y-Leon F, et al:** An unusual variety of atrioventricular nodal reentry due to retrograde dual atrioventricular nodal pathways. Circulation 56:50–59, 1977
17. **Denes P, Wu D, Amat-y-Leon F, et al:** The determinants of atrioventricular nodal reentrance with premature atrial stimulation in patients with dual A-V nodal pathways. Circulation 56:253–259, 1977
18. **Sung RJ, Castellanos A, Styperek J, et al:** Initiation of an unusual form of A-V nodal reentrant tachycardia by atrial and ventricular premature stimulation (abstr). Circulation 56:Suppl III:III-105, 1977
19. **Schuilenburg RM, Durrer D:** Ventricular echo beats in the human heart elicited by induced ventricular premature beats. Circulation 11:337–347, 1969
20. **Satake S, Heijima K, Sakamoto Y, et al:** Demonstration of bidirectional dual A-V nodal pathways in the same patient. J Electrocardiol 10:71–76, 1977
21. **Sung RJ, Castellanos A, Mallon SM, et al:** Mode of initiation of reciprocating tachycardia during programmed ventricular stimulation in the Wolff-Parkinson-White syndrome. With reference to various patterns of ventriculo-atrial conduction. Am J Cardiol 40:24–31, 1977
22. **Sung RJ, Gelband H, Castellanos A, et al:** Clinical and electrophysiological observations in patients with concealed accessory A-V bypass tracts. Am J Cardiol 40:839–847, 1977
23. **Scherlag BJ, Lau SH, Helfant RH, et al:** Catheter technique for recording His bundle activity in man. Circulation 39:13–18, 1969
24. **Castellanos A Jr, Castillo CA, Agha AS, et al:** His bundle electrograms in patients with short P-R intervals, narrow QRS complexes, and paroxysmal tachycardias. Circulation 43:667–678, 1971
25. **Akhtar M, Damato AN, Batsford WP, et al:** A comparative analysis of antegrade and retrograde conduction patterns in man. Circulation 52:766–778, 1975
26. **Wellens HJJ, Durrer D:** Patterns of ventriculo-atrial conduction in Wolff-Parkinson-White syndrome. Circulation 49:22–31, 1974
27. **Svenson RH, Miller HC, Gallagher JJ, et al:** Electrophysiological evaluation of the Wolff-Parkinson-White syndrome: problems in assessing antegrade and retrograde conduction over the accessory pathway. Circulation 52:552–562, 1975
28. **Rosenbluuth A:** Ventricular "echoes". Am J Physiol 195:53–60, 1958
29. **Moe GK, Preston JB, Burlington H:** Physiologic evidence for a dual A-V transmission system. Circ Res 4:357–375, 1956
30. **Mendez C, Han J, Garcia de Jalon PD, et al:** Some characteristics of ventricular echoes. Circ Res 16:562–581, 1965
31. **Mendez C, Moe GK:** Demonstration of a dual A-V nodal conduction system in the isolated rabbit heart. Circ Res 19:378–393, 1966
32. **Coumel P, Cabrol C, Fabiato A, et al:** Tachycardie permanente par rhythme réaproque. I. Preuves du diagnostic par stimulation auriculaire et ventriculaire. Arch Mal Coeur 60:1830–1849, 1967
33. **Castillo CA, Castellanos A Jr:** Retrograde activation of the His bundle during intermittent paired ventricular stimulation in the human heart. Circulation 43:1079–1092, 1970
34. **Castellanos A, Sung RJ, Ghahramani A, et al:** The retrograde His bundle deflection: its recognition and value in the analysis of tachyarrhythmias induced by stimulation on the T wave. Eur J Cardiol 4:295–302, 1976
35. **Akhtar M, Damato AN, Batsford WP, et al:** Demonstration of reentry within the His-Purkinje system in man. Circulation 50: 1150–1162, 1974
36. **Akhtar M, Damato AN, Ruskin JN, et al:** Characteristics and coexistence of two forms of ventricular echo phenomena. Am Heart J 92:174–182, 1976
37. **Denes P, Wu D, Dhingra RC, et al:** The effects of cycle length on cardiac refractory periods in man. Circulation 49:32–41, 1974
38. **Wu D, Denes P, Amat-y-Leon F, et al:** Clinical, electrocardiographic and electrophysiologic observations in patients with paroxysmal supraventricular tachycardia. Am J Cardiol 41:1045–1051, 1978

Sustained Ventricular Tachycardia: Evidence for Protected Localized Reentry

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The components of the reentrant circuit were evaluated in 26 patients in whom sustained ventricular tachycardia could be reproducibly initiated or terminated, or both. Observations suggesting that the proximal His-Purkinje system was not a requisite component included (1) lack of requirement for retrograde His-Purkinje delay or bundle branch reentry, or both, for initiation of the tachycardia; (2) anterograde depolarization of the His bundle during ventricular tachycardia without alteration of the QRS configuration or cycle length; and (3) the presence of random retrograde His potentials during the tachycardia. Evidence that the reentrant circuit was localized to a small area of the ventricles included (1) the ability to capture large segments of the ventricles transiently or continuously with ventricular stimulation without affecting the tachycardia, and (2) the occurrence of intermittent or continuous *supraventricular* capture either spontaneously or with atrial pacing without effect on the tachycardia. These findings suggest that the reentrant circuit must be small, electrocardiographically silent and relatively protected.

The mechanism of most episodes of sustained ventricular tachycardia is thought to be reentry.[1–7] However, the extent of the reentrant circuit within the ventricles has heretofore not been examined in man. Successful abolition of ventricular tachycardia after aneurysmectomy[8–10] suggests that the reentrant circuit is relatively circumscribed and small, whereas abolition of the arrhythmia after large transmyocardial incisions has led some investigators[11–13] to propose a macroreentrant circuit, possibly incorporating the bundle branches or large areas of ventricular myocardium. This study was undertaken to evaluate the size and components of the reentrant circuit.

Material and Methods

Patients: We evaluated 26 patients in whom ventricular tachycardia could be reproducibly initiated or terminated, or both, with programmed stimulation (Table I). The studies were performed with patients in the nonsedated postabsorptive state after they had given informed consent. Antiarrhythmic agents were withheld for 24 to 48 hours before the procedure. Fifteen patients had coronary artery disease, and 13 of these had a ventricular aneurysm. Four patients were studied within 6 weeks of a myocardial infarction.

Procedures: Three to six electrode catheters were inserted percutaneously or with a cutdown procedure and fluoroscopically positioned in the heart. The number of recording sites varied but usually included the right atrium, atrioventricular (A-V) junction at the His bundle recording site, right ventricle at the apex, septum and inflow or outflow tract, or both; the left ventricle at the apex, septum, lateral wall or base, or both; and the coronary sinus. Quadripolar electrode catheters were used when it was necessary to provide both recording and stimulation from a given site; in such cases one pair of electrodes was used for recording and the other for stimulation. A tripolar catheter was used to obtain the His bundle and local ventricular electrogram at the A-V junction.

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TABLE I

Summary of 25 Cases of Ventricular Tachycardia

Case no.	Age (yr) & Sex	Cardiac Diagnosis	ECG	Retrograde His-Purkinje System Delay	BBR	Random Retrograde His	Ventricular Capture		Supraventricular Capture	
							VPD	VP	Sinus	AP
1	18M	None	WNL	+	+	+	+	−	+	+
2	52M	ASHD, Vent An	ASMI, LAH	+	+	+	*	*	*	*
3	57M	ASHD, Vent An	IMI, ASMI	+	+	+	+	+	+	+
4	52M	ASHD, Vent An	IMI, ASMI	−	−	+	+	+	+	+
5	61M	CM	RBBB	+	+	−	+	−	−	−
6	67M	None	WNL	+	−	−	*	*	*	*
7	73F	HCVD	LVH	+	−	−	*	*	*	*
8	54F	ASHD	NTMI	+	+	−	*	*	*	*
9	49M	ASHD	ASMI, IACD	−	−	−	+	−	−	−
10	59M	ASHD, Vent An	ASMI, AVB, RBBB, LAH	+	−	+	+	+	+	+
11	22M	CAA	Inc RBBB	−	−	−	+	−	+	−
12	51M	ASHD, Vent An	IMI, IVCD	−	−	+	+	−	+	+
13	46M	None	WNL	+	+	+	+	−	+	−
14	64M	None	Pseudo IMI*	−	−	+	+	+	−	−
15	63M	ASHD, Vent An	AMI	+	+	+	+	−	+	−
16	63M	ASHD, Vent An	IMI	+	+	−	+	+	−	−
17	53F	RHD, Vent An ASHD	RBBB, ASMI	−	−	+	+	−	+	−
18	21M	IHSS	AVB, LVH, IVCD	+	−	+	+	+	+	−
19	37M	None	WNL	+	+	−	+	−	−	−
20	60F	ASHD, Vent An	AMI	+	+	+	+	−		
21	33M	ASHD, Vent An	IMI	+	+	+	+	+	−	−
22	56M	ASHD, Vent An	AMI, IVCD	−	−	+	+	+	+	+
23	67M	ASHD, Vent An	IMI	+	+	−	+	−	+	−
24	62M	CM	Inc LBBB, AVB	+	+	−	+	+	−	−
25	57M	HCVD	RBBB, LAH	+	−	−	+	−	+	−

* Stimulation not performed.

AMI = anterior myocardial infarction; AP = atrial pacing; ASHD = atherosclerotic heart disease; ASMI = anteroseptal myocardial infarction; AVB = first degree atrioventricular block; BBR = bundle branch reentry; CAA = coronary arterial anomaly; CM = cardiomyopathy; ECG = electrocardiogram; HCVD = hypertensive cardiovascular disease; IACD = intraatrial conduction; Inc = incomplete; LBBB = left bundle branch block; IHSS = idiopathic hypertrophic subaortic stenosis; IMI = inferior myocardial infarction; IVCD = intraventricular conduction disturbance; LAH = left anterior hemiblock; LVH = left ventricular hypertrophy; NTMI = nontransmural myocardial infarction; RHD = rheumatic heart disease; RBBB = right bundle branch block; Vent An = ventricular aneurysm; VP = ventricular pacing; VPD = ventricular premature depolarization; WNL = within normal limits.

+ = yes; − = no.

Programmed electrical stimulation was performed according to our previously published protocol,[7] using a specially designed digital stimulator and isolated constant current source (Bloom Associates Ltd., Narberth, Pennsylvania). The stimuli were rectangular pulses 1 msec in duration and twice diastolic threshold (0.75 to 2 ma). Intracardiac recordings from several sites (usually from the right atrium, right ventricular apex and A-V junction and in 22 patients from additional sites within the right ventricle or coronary sinus, or both) were simultaneously recorded with two or three surface electrocardiographic leads. Intracardiac electrograms were filtered at 40 to 500 hertz. The data were stored on magnetic tape (Honeywell 5600) and later retrieved on photographic paper at speeds of 150 to 200 mm/sec.

The role of the proximal His-Purkinje system was assessed by analyzing the relation of the initiation and maintenance of the tachycardia to the timing and appearance of His potentials or bundle branch reentry, or both. The extent of ventricular myocardium participating in the tachycardia circuit was evaluated by analyzing the effect of atrial or ventricular stimulation, or both, on ventricular depolarization during the tachycardia. This analysis was facilitated by recording multiple ventricular electrograms, which always included simultaneous electrograms from at least one site in the right and left ventricles.

Results

Role of Proximal His-Purkinje System

Several observations provided evidence that the proximal His-Purkinje system was not required for initiation or maintenance of the tachycardia: Retrograde His-Purkinje delay was observed in 19 patients; in 12 of these the tachycardia could be initiated before as well as simultaneously with the development of this delay; in the remaining 7, the tachycardia was initiated in the presence of various degrees of conduction delay. Bundle branch reentry,[14] observed in 14 patients, was not required for initiation of the tachycardia in any patient (Fig. 1). Seven patients did not have retrograde His-Purkinje conduction delay and 12 had no bundle branch reentry.

In seven patients during ventricular tachycardia anterograde depolarization of the His bundle occurred without a change in the QRS comfiguration or cycle length of the arrhythmia (Fig. 2). This observation suggests that the reentrant circuit is confined to an area below the recording site of the His deflection. In addition, in 14 patients random retrograde His potentials

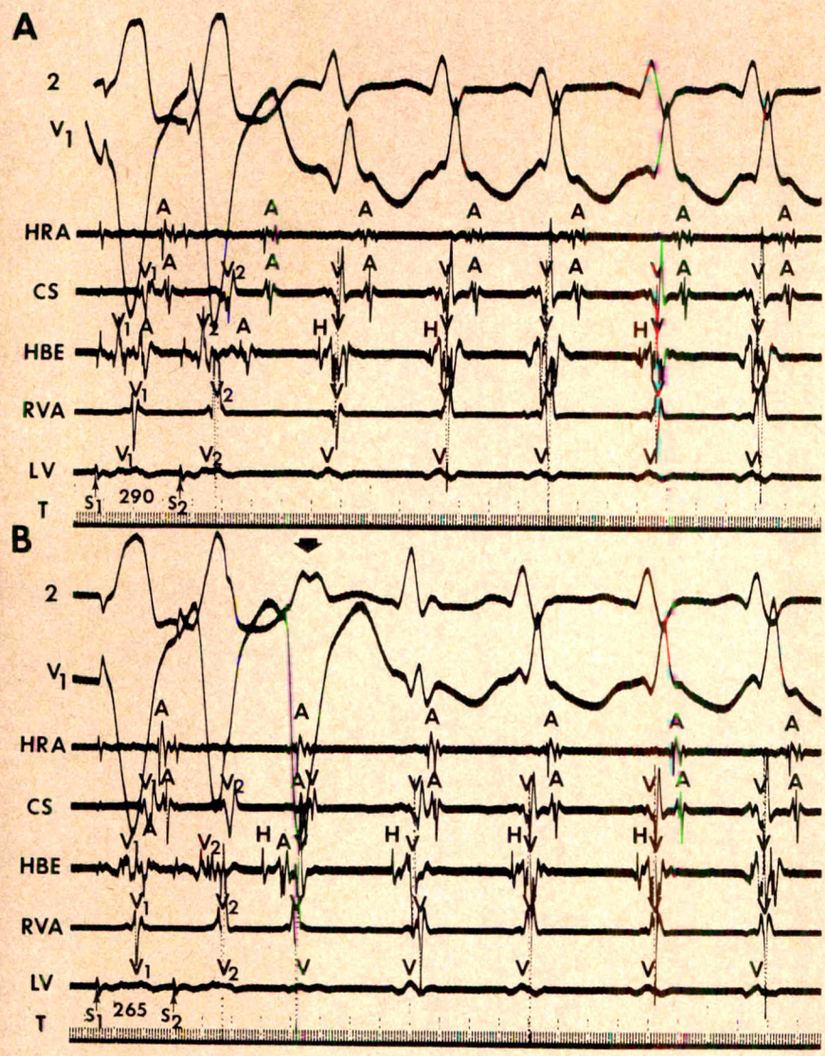

FIGURE 1. Case 1. Initiation of ventricular tachycardia in presence or absence of bundle branch reentry or retrograde His-Purkinje delay. **From top to bottom** are electrocardiographic leads II (2) and V_1 and electrograms from the high right atrium (HRA), coronary sinus (CS), His bundle area (HBE), right ventricular apex (RVA), left ventricular apex (LV) and time lines (T). In **panel A** at a coupling interval (S_1–S_2) of 290 msec, ventricular tachycardia is initiated in the absence of retrograde His-Purkinje delay (no V-H prolongation) or bundle branch reentry. In **panel B** at a coupling interval of 265 msec, ventricular tachycardia occurs after the development of both retrograde His-Purkinje delay and bundle branch reentry (**broad arrow**). Random His potentials are noted during the tachycardia: In panel **A** they appear with a 2:1 frequency; in panel **B** there is a changing relation with the QRS complex. The site of stimulation is the right ventricular outflow tract (not shown).

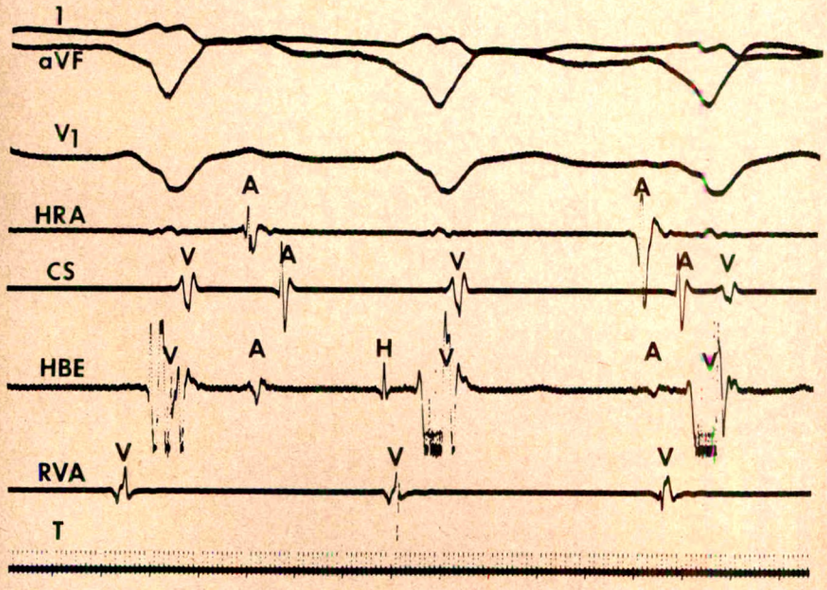

FIGURE 2. Case 4. Anterograde depolarization of the His bundle during ventricular tachycardia. **From top to bottom** are electrocardiographic leads I (1), aVF and V_1 and electrograms from the high right atrium (HRA), coronary sinus (CS), His bundle area (HBE), right ventricular apex (RVA) and time lines (T). Ventricular tachycardia with atrioventricular dissociation is present. The first atrial impulse conducts through the His bundle but fails to alter the tachycardia.

were observed during the tachycardia. In each of these 14 patients there was no relation between the appearance or timing of these His deflections and the rate or pattern of the tachycardia (Fig. 1). In the remaining 12 patients no retrograde His potentials were observed.

Extent of ventricular participation: Several observations suggested that the tachycardia circuit was localized to a small area within the ventricles. In 22 patients large segments of one or both ventricles could be captured by ventricular extrastimuli without effect on the tachycardia. In the remaining four patients (Cases 2, 6, 7 and 8) hemodynamic or electrical deterioration, or both, necessitated cardioversion before ventricular stimulation could be performed. In each of

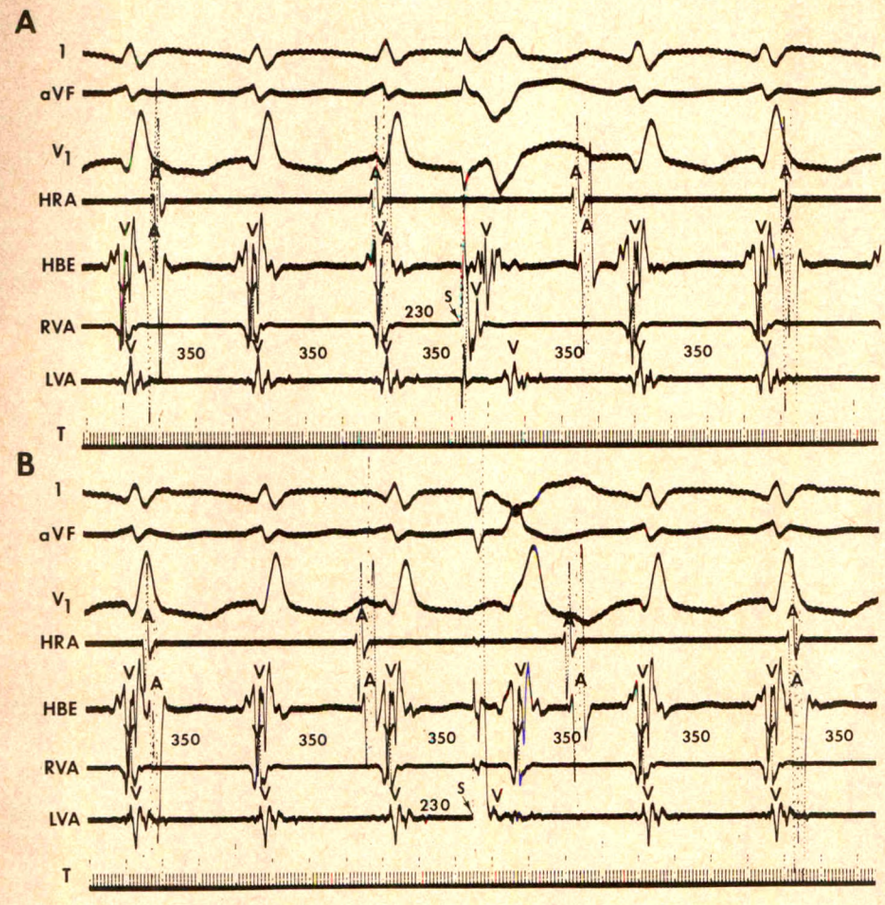

FIGURE 3. Case 6. Effect of right and left ventricular stimulation during ventricular tachycardia. **From top to bottom** are leads I (1), aVF and V_1 and electrograms from the high right atrium (HRA), His bundle area (HBE), right ventricular apex (RVA), left ventricular apex (LVA) and time lines (T). Ventricular tachycardia is present at a cycle length of 350 msec. In panel **A** a right ventricular extrastimulus (**S, arrow**) results in capture of the right ventricular apex and His bundle electrogram and changes the QRS configuration. The tachycardia is not affected because the left ventricular apical electrogram is unaltered. In **panel B** a left ventricular stimulus captures the left ventricular apex and changes the QRS complex but fails to affect the tachycardia.

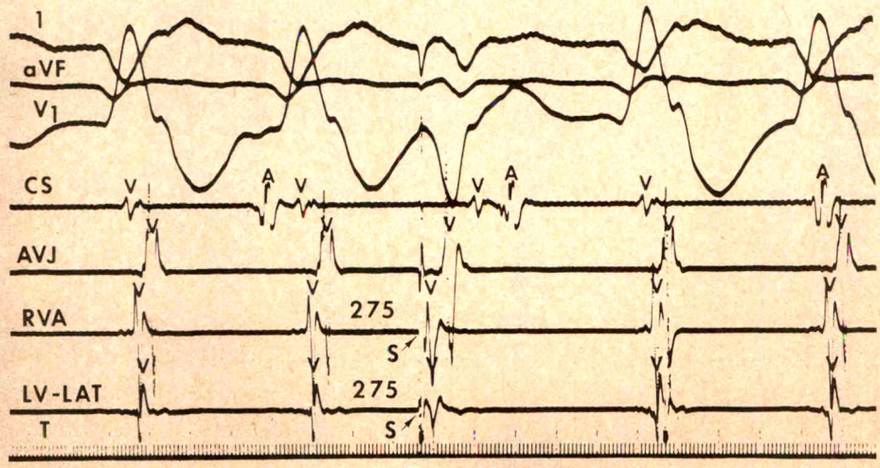

FIGURE 4. Case 15. Biventricular stimulation during ventricular tachycardia. **From top to bottom** are electrocardiographic leads I (1), aVF, V_1 and electrograms from the coronary sinus (CS), atrioventricular junction (AVJ), right ventricular apex (RVA), the lateral edge of a left ventricular apical aneurysm (LV-LAT) and time lines (T). After two beats of ventricular tachycardia simultaneous right and left ventricular stimuli (**S, arrow**) are delivered at a coupling interval of 275 msec, resulting in biventricular capture without effect on the tachycardia. A full compensatory pause follows the extrastimuli.

the 22 patients in whom ventricular stimulation could be accomplished during the tachycardia, a single ventricular premature depolarization was able to capture the stimulated ventricle (and in 13 patients part of the contralateral ventricle) without terminating the arrhythmia. In six patients single ventricular premature depolarizations from both the right and the left ventricle failed to terminate the arrhythmia (Fig. 3). Moreover, in five patients simultaneous stimulation of both ventricles resulting in capture (as defined by earlier than expected right and left ventricular electrograms and change in QRS configuration) failed to terminate the

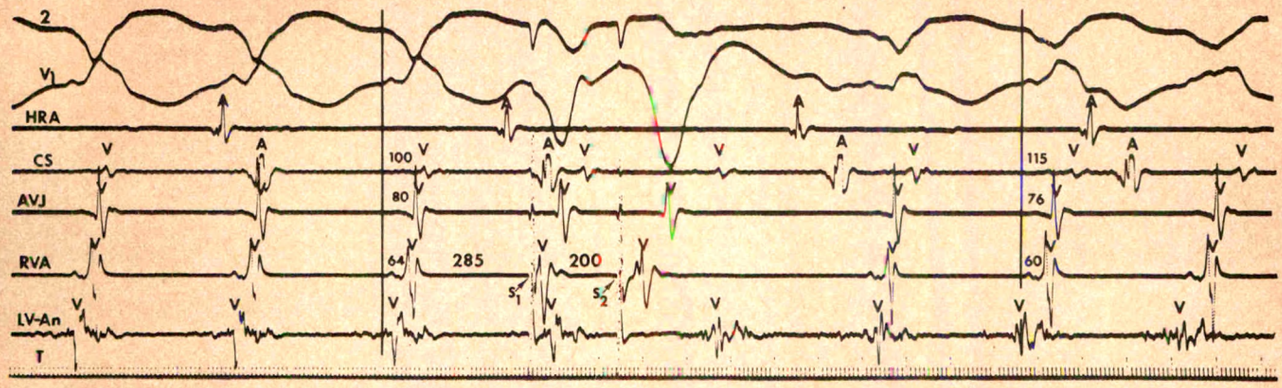

FIGURE 5. Case 15. Mechanism of protection during ventricular tachycardia. The panel is organized as in Figure 4 except that the left ventricular catheter has been moved to within the aneurysm (LV-An) and the electrocardiographic leads are II (2) and V_1. A high right atrial electrogram (HRA) is also shown. During ventricular tachycardia two right ventricular extrastimuli are delivered, resulting in capture (note the changed QRS complex) without termination of the tachycardia. Continuing activity within the aneurysm is seen despite biventricular capture. However, slight changes in ventricular activation have occurred.

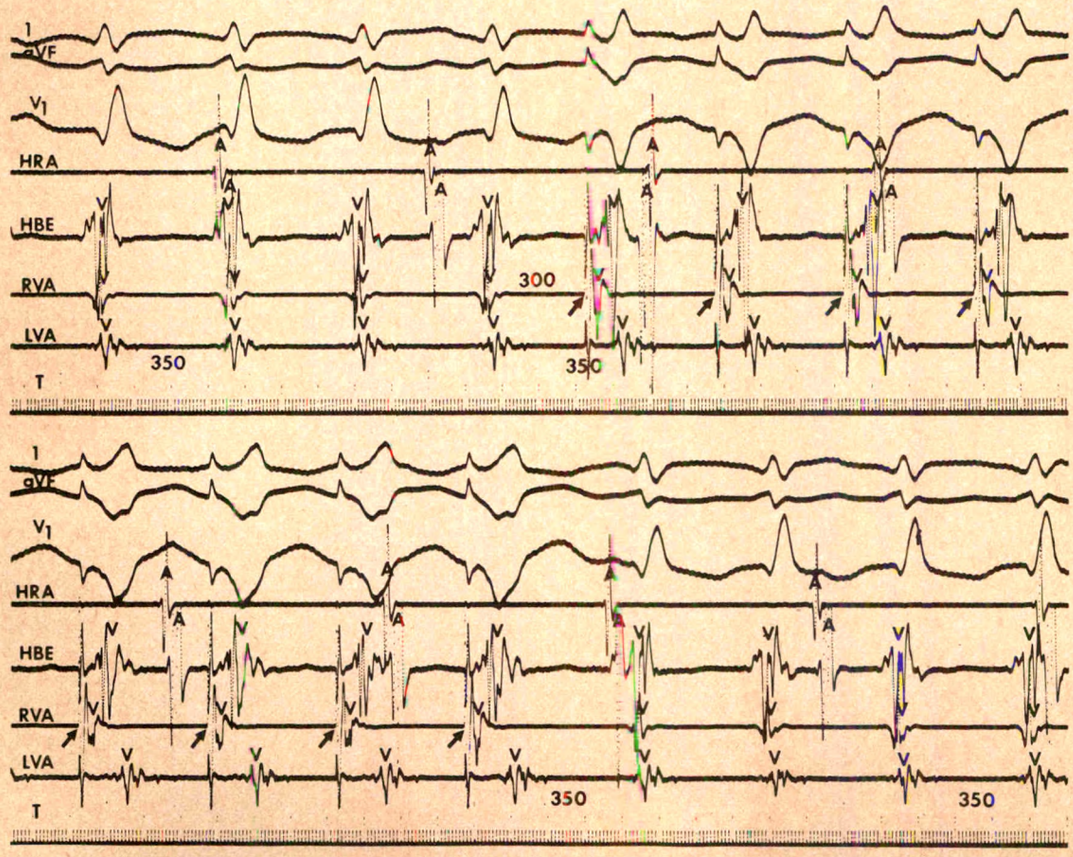

FIGURE 6. Case 16. Failure of ventricular pacing to alter ventricular tachycardia. The panel is organized as in Figure 3. Ventricular tachycardia is present at a cycle length of 350 msec. Right ventricular pacing (**arrows**) is begun after the fourth complex (**upper panel**), resulting in ventricular capture (change in QRS complex). When pacing is discontinued (**bottom panel**) the tachycardia is still present. During right ventricular pacing the electrogram from the left ventricular apex remains unaffected.

arrhythmia (Fig. 4). In each instance of single or biventricular capture full compensatory pauses followed the stimulated complex, suggesting that the tachycardia was unaffected and that the reentrant circuit was not penetrated. In one patient repositioning the recording left ventricular catheter to a site within an aneurysm provided an explanation for these findings by demonstrating continuing uninterrupted activity despite capture of other ventricular sites by double ventricular extrastimuli (Fig. 5). In 10 patients ventricular pacing resulting in continuous ventricular capture failed to terminate the arrhythmia (Fig. 6). In 6 of these 10 patients ventricular pacing was incapable of initiating the tachycardia; thus the possibility of termination and immediate reinitiation of the tachycardia by pacing was excluded.

In 13 patients intermittent partial or complete supraventricular captures occurred without termination of the arrhythmia. Each of the complete captures was associated with QRS and H-V intervals comparable with those occurring during sinus rhythm (Fig. 7). Moreover, in six patients atrial pacing could produce continuous supraventricular capture with normalization of the QRS and H-V intervals without termination of the arrhythmia (Fig. 8). Because atrial pacing could not initiate the tachycardia the possibility of termination followed by reinitiation was excluded. In addition, in six cases sinus captures after delivery of ventricular extrastimuli during the tachycardia occurred without interruption of the arrhythmia (Fig. 9).

Discussion

Most episodes of sustained recurrent ventricular tachycardia are thought to be due to reentry on the basis of reproducible initiation or termination, or both.[1–7] Although the reentrant pathways have not been precisely characterized in man, it has been suggested that they may include the bundle branches or large areas of the ventricular myocardium, or both.[1,5,6,11–13] In contrast, our study suggests that the reentrant circuit is both localized and relatively protected.

Proof that the His bundle and proximal His-Purkinje system are not incorporated in the reentrant pathway: Such proof requires demonstration that depolarization of these structures has no effect on the tachycardia. Observations suggesting that the proximal His-Purkinje system did not participate in the reentrant circuit included: (1) lack of requisite retrograde His-Purkinje conduction delay for initiation of the tachycardia, (2) absence of bundle branch reentry as a prerequisite for development of the tachycardia, (3) occurrence of infra-His block of impulses conducted in anterograde manner with no effect on the tachycardia, and (4) appearance of random retrograde His potentials during the tachycardia. If macroreentry involving the proximal conducting system were the mechanism of this arrhythmia, consistent His bundle electrograms with a normal or greater than normal H-V interval should be observed.[14] Recently, Wellens et al.[4] similarly concluded that activation of the His-Purkinje system is a secondary phenomenon in the great majority of reentrant ventricular tachycardias.

Several other observations suggested that the tachycardia was localized to a small area within the ventricles. These included (1) ability to depolarize prematurely both ventricles either intermittently or consistently with ventricular stimulation, and (2) occurrence of intermittent or persistent supraventricular capture with normalization of the QRS pattern with no effect on the tachycardia. The depolarization and capture of large portions of the ventricles with no effect on the tachycardia suggests that the reentrant circuit may be relatively protected but cannot necessarily prove that the circuit is confined to a small area of the ventricles. However, the production of a QRS complex indistinguishable from that of sinus rhythm during the tachy-

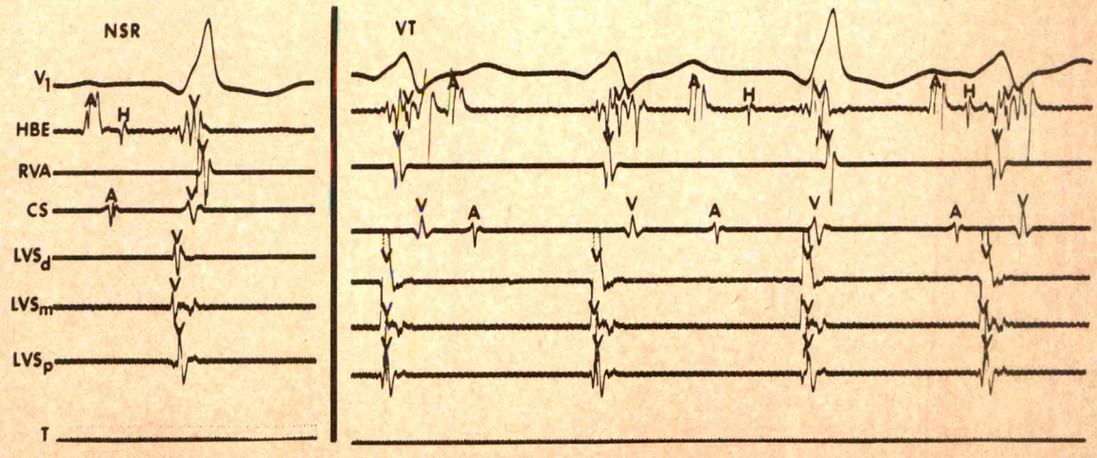

FIGURE 7. Case 10. Spontaneous supraventricular capture during ventricular tachycardia. From top to bottom are electrocardiographic lead V_1 and electrograms from the His bundle (HBE), right ventricular apex (RVA), coronary sinus (CS), distal, mid and proximal left ventricular apex (LVS_d), LVS_m, LVS_p, respectively) and time lines (T). On the left is a sinus complex (NSR) and on the right ventricular tachycardia (VT) with atrioventricular dissociation is present. After the second complex of ventricular tachycardia a sinus capture occurs, resulting in normalization of the QRS and H-V intervals without interruption of the tachycardia.

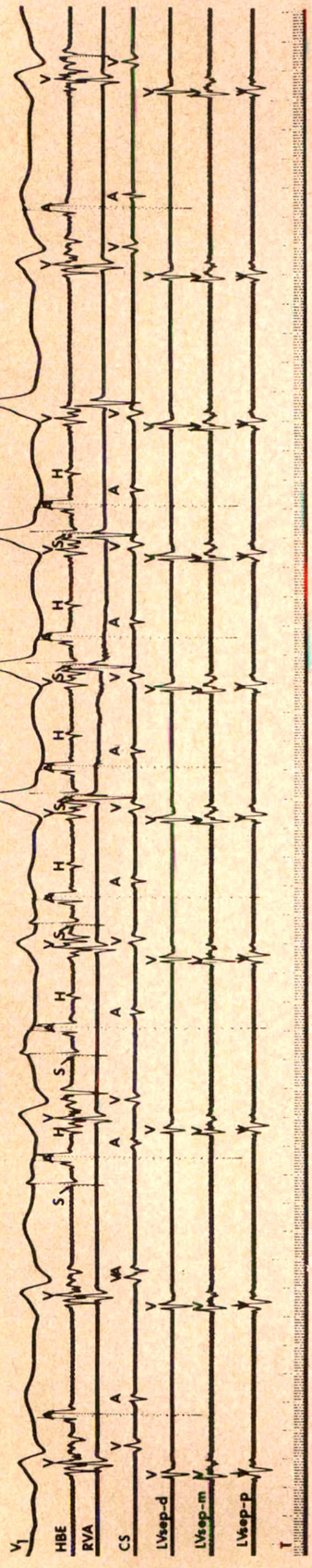

FIGURE 8. Case 10. Failure of continuous supraventricular capture by atrial pacing to terminate ventricular tachycardia. The panel is arranged as in Figure 7. Atrial pacing, begun (**arrows**) during ventricular tachycardia, results in 1:1 supraventricular capture. When pacing is discontinued, the tachycardia immediately resumes. See text. LV_{sep-d}, LV_{sep-m} and LV_{sep-p} = distal, mid and proximal left ventricular apex, respectively.

cardia without influence on the arrhythmia suggests that the site of reentry must be small and indeed electrocardiographically silent. If the reentrant circuit were composed of a large area of the ventricles, true supraventricular captures with normalization of the QRS complexes would be virtually impossible without termination of the arrhythmia. This finding also suggests that the QRS configuration during the tachycardia is merely a consequence of ventricular activation from a circumscribed process. The ability of the tachycardia to continue despite atrial or ventricular capture, or both, can be termed "concealed reentry," as suggested by El-Sherif et al.[15,16]

Role of reentry as mechanism for recurrent ventricular tachycardia: Recent evidence has raised the possibility that oscillatory afterpotentials may be the underlying basis of some triggered arrhythmias.[17–20] The ability to distinguish such triggered automaticity, which has been described only in vitro under experimental conditions, from a small reentrant focus is limited. However, several lines of evidence suggest that reentry is the underlying mechanism for recurrent ventricular tachycardia: (1) In the 11 patients in whom the tachycardia could be initiated with a single ventricular premature depolarization there was an inverse relation between the coupling interval of the premature stimulus and the interval to the first complex of the tachycardia. This finding, which is analogous to findings in patients with A-V nodal reentrant supraventricular tachycardia,[21] has not been observed with triggered rhythms and supports the hypothesis of reentry. (2) The ability to terminate ventricular tachycardia immediately with programmed stimulation was demonstrated in each of our patients. In published records of triggered automaticity usually one to three additional complexes follow the extrastimulus that terminates the arrhythmia.[19] (3) Verapamil, which has been demonstrated to abolish triggered automaticity,[18,20] and propranolol, which might potentially antagonize catecholamine-dependent triggered automaticity, have not been effective in recurrent ventricular tachycardia.[22] On the other hand, drugs such as procainamide and quinidine, which have proved effective in the management of this arrhythmia, have not been shown to affect abnormal calcium-dependent automaticity.[23] (4) In three patients we were able to demonstrate that the initiation and maintenance of ventricular tachycardia was dependent upon fragmentation and conduction delays spanning diastole,[24] findings analogous to those of El-Sherif et al., in animal preparations.[15,16] Such continuous fragmented and fractionated activity strongly supports consideration of reentry as the underlying basis for the tachycardia. (5) Successful abolition of ventricular tachycardia by transmyocardial incision in areas manifesting slow conduction is most consistent with a reentrant basis for the arrhythmia.[11–13] Thus, the bulk of evidence still suggests that sustained ventricular tachycardia that can be reproducibly initiated or terminated, or both, with programmed stimulation is due to reentry. However, we cannot totally exclude in all

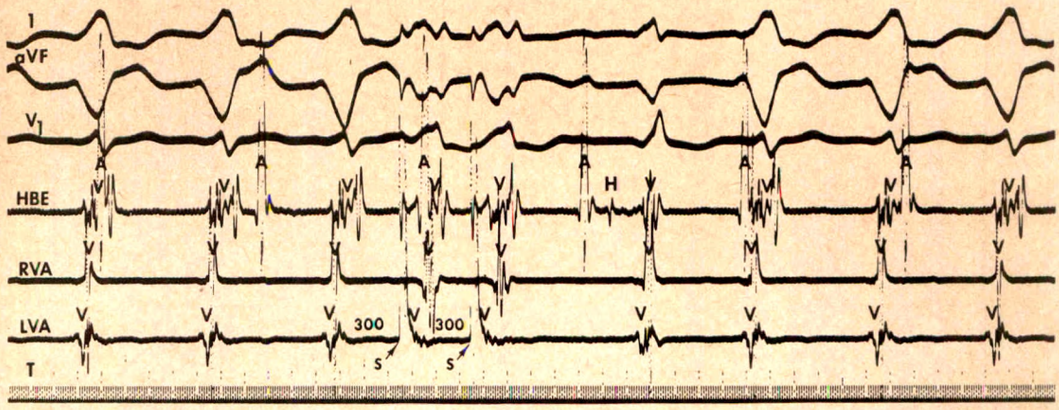

FIGURE 9. Case 10. Failure of consecutive ventricular and supraventricular capture to terminate ventricular tachycardia. **From top to bottom** are electrocardiographic leads I (1), aVF and V_1 and electrograms from the His bundle area (HBE), right ventricular apex (RVA), left ventricular apex (LVA) and time lines (T). After three tachycardia complexes two left ventricular extrastimuli (S, **arrows**) are delivered, resulting in biventricular capture followed by a sinus capture (**vertical arrow**), without termination of the arrhythmia.

patients triggered automaticity as a mechanism of ventricular tachycardia.

Implications: The use of multiple recordings from both ventricles in coordination with programmed ventricular stimulation during ventricular tachycardia can provide insight into the mechanisms of the arrhythmia. Using these techniques we have shown that neither the proximal His-Purkinje system nor the major portions of the ventricles are required to initiate or sustain ventricular tachycardia. Furthermore, intermittent or continuous normalization to supraventricular complexes without termination of the arrhythmia suggests that the site of reentry must be small, electrocardiographically silent and relatively protected.

Acknowledgment

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References

1. **Wellens HJJ, Schuilenburg RM, Durrer D:** Electrical stimulation of the heart in patients with ventricular tachycardia. Circulation 46:216–226, 1972
2. **Wellens HJJ, Lie KI, Durrer D:** Further observations on ventricular tachycardia as studied by electrical stimulation of the heart. Chronic recurrent ventricular tachycardia and ventricular tachycardia during acute myocardial infarction. Circulation 49:647–653, 1974
3. **Wellens HJJ:** Observations on the pathophysiology of ventricular tachycardia in man. Arch Intern Med 135:473–479, 1975
4. **Wellens HJJ, Düren DR, Lie KI:** Observations on mechanisms of ventricular tachycardia in man. Circulation 54:237–244, 1976
5. **Spurrell RAJ, Sowton E, Deuchar DC:** Ventricular tachycardia in 4 patients evaluated by programmed electrical stimulation of heart and treated in 2 patients by surgical division of the anterior radiation of left bundle-branch. Br Heart J 35:1014–1025, 1973
6. **Guerot CL, Vateri PA, Castello-Fenoy A, et al:** Tachycardia par reentri de branche a branche. Arch Mal Coeur 67:1–8, 1975
7. **Josephson ME, Horowitz LN, Farshidi A, et al:** Recurrent sustained ventricular tachycardia: I. Mechanisms. Circulation 57:431–439, 1978
8. **Kenaan G, Mendez AM, Zubiate P, et al:** Surgery for ventricular tachycardia unresponsive to medical treatment. Chest 64:574–578, 1973
9. **Magidson O:** Resection of postmyocardial infarction ventricular aneurysms for cardiac arrhythmias. Dis Chest 56:211–218, 1969
10. **Gallagher JJ, Oldham HN, Wallace AG, et al:** Ventricular aneurysm with ventricular tachycardia. Report of a case with epicardial mapping and successful resection. Am J Cardiol 35:696–700, 1975
11. **Fontaine G, Guiraudon G, Frank R, et al:** Epicardial mapping and surgical treatment in six cases of resistant ventricular tachycardia not related to coronary artery disease. In, The Conduction of the Heart, chap 30 (Wellens HJJ, Lie KI, Janse MJ, ed). Philadelphia, Lea & Febiger, 1976, p 545–563
12. **Fontaine G, Guiraudon G, Frank R, et al:** Stimulation studies and epicardial mapping in ventricular tachycardia: study of mechanisms and selection for surgery. In, Reentrant Arrhythmias, chap 24 (Kulbertus HE, ed). Baltimore, University Park Press, 1976, p 334–350
13. **Spurrell RAJ, Yates A, Thorburn CW, et al:** Surgical treatment of ventricular tachycardia after epicardial mapping studies. Br Heart J 37:115–126, 1975
14. **Akhtar M, Damato AN, Batsford WP, et al:** Demonstration of reentry within the His-Purkinje system in man. Circulation 50: 1150–1162, 1974
15. **El-Sherif N, Scherlag BJ, Lazzara R, et al:** Re-entrant arrhythmias in the late myocardial infarction period. I. Conduction characteristics in the infarct zone. Circulation 55:686-702, 1977
16. **El-Sherif N, Hope RR, Scherlag BJ, et al:** Re-entrant arrhythmias in the late myocardial infarction period. II. Patterns of initiation and termination. Circulation 55:702–719, 1977
17. **Cranefield PF, Aronson RS:** Initiation of sustained rhythmic activity by single propagated action potentials in canine cardiac Purkinje

fibers exposed to sodium-free solution or to ouabain. Circ Res 34:477–481, 1974
18. **Cranefield PJ:** The slow response and cardiac arrhythmias. In, The Conduction of the Cardiac Impulse, chap 6. Mount Kisco, NY, Futura, 1975, p 199–212
19. **Ferrier GR, Saunders JH, Mendez C:** A cellular mechanism for the generation of ventricular arrhythmias by acetylstrophanthidin. Circ Res 32:600–609, 1973
20. **Wit AL, Cranefield PF:** Triggered activity in cardiac muscle fibers of the simian mitral valve. Circ Res 38:85–98, 1976
21. **Goldreyer BN, Bigger JT Jr:** The site of reentry in paroxysmal supraventricular tachycardia in man. Circulation 43:15–26, 1971
22. **Wellens HJJ, Bär FWHM, Lie KI, et al:** Effect of procainamide, propranolol and verapamil on the mechanism of tachycardia in patients with chronic recurrent ventricular tachycardia. Am J Cardiol 40:579–585, 1977
23. **Hardoff AJ, Edie R, Malm JR, et al:** Electrophysiologic properties and response to pharmacologic agents of fibers from diseased human atria. Circulation 54:774–779, 1976
24. **Josephson ME, Horowitz LN, Farshidi A:** Continuous local electrical activity: a mechanism of recurrent ventricular tachycardia. Circulation 57:659–665, 1978

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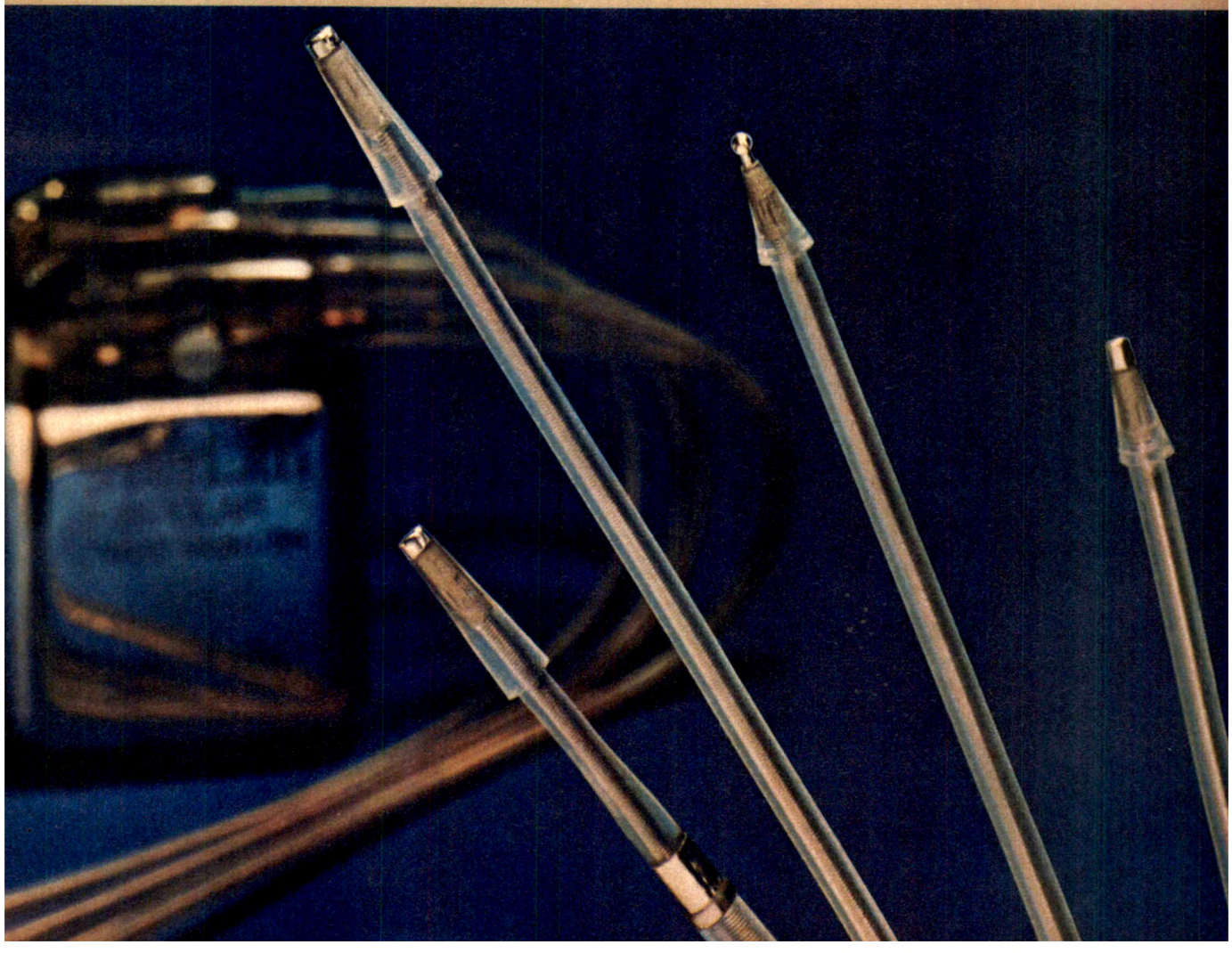

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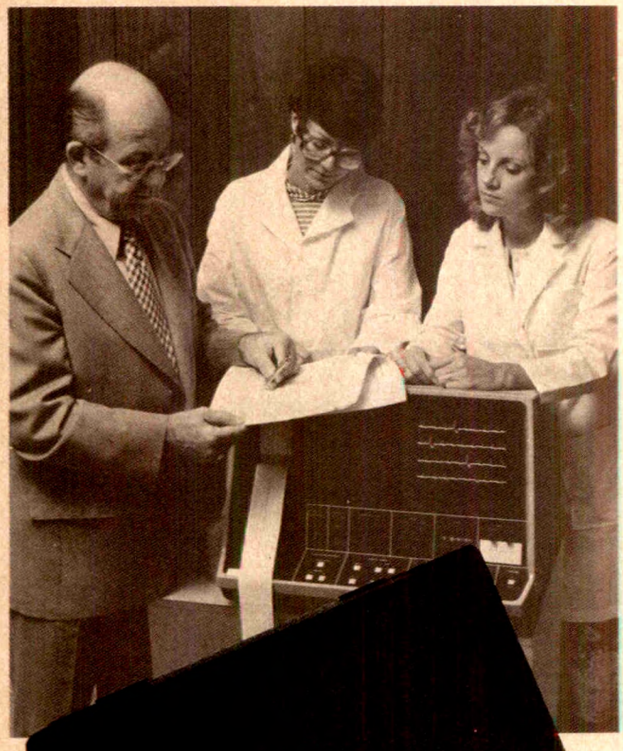

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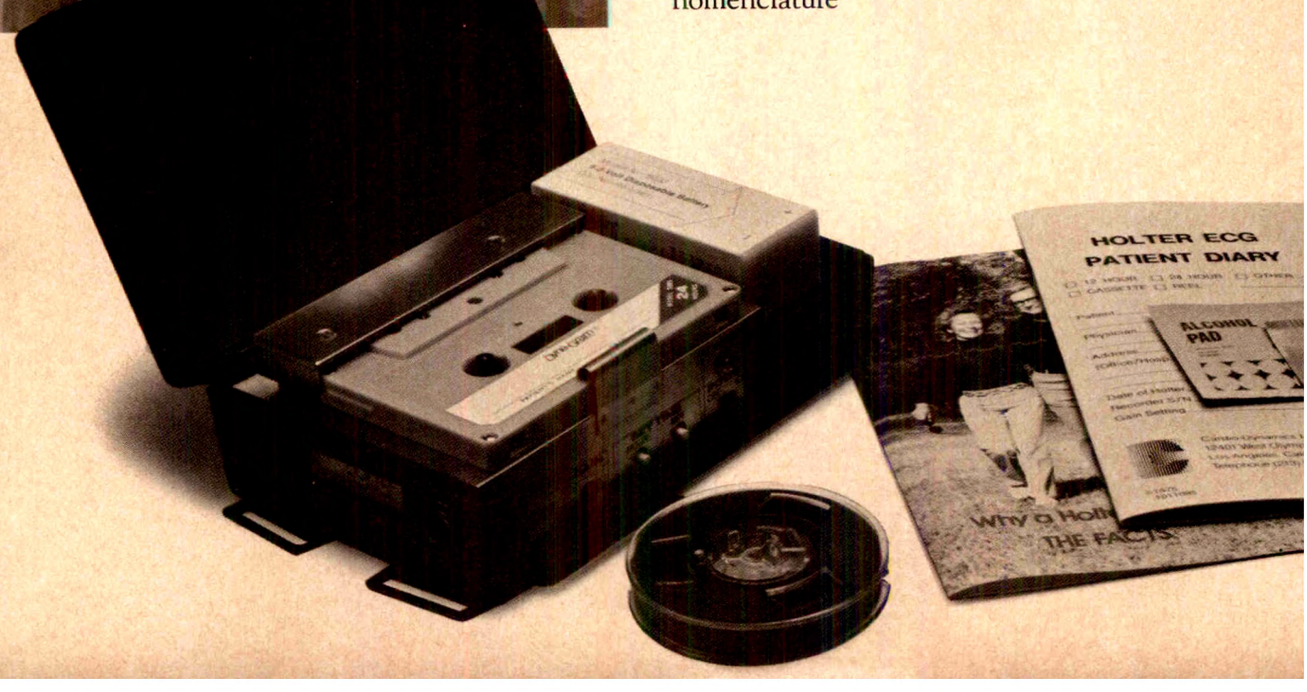

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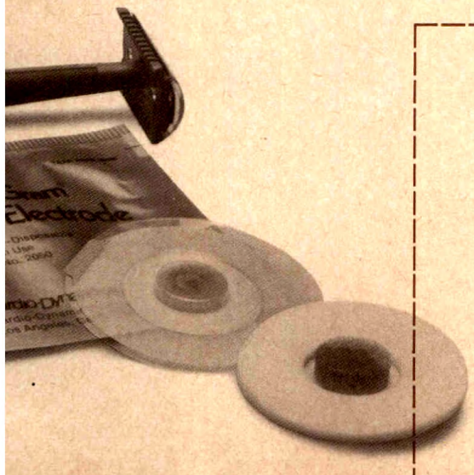

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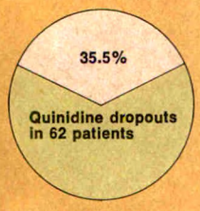

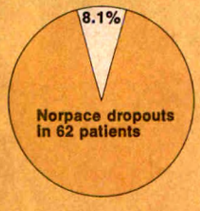

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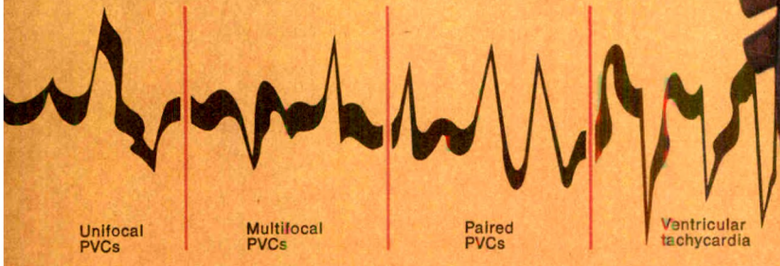

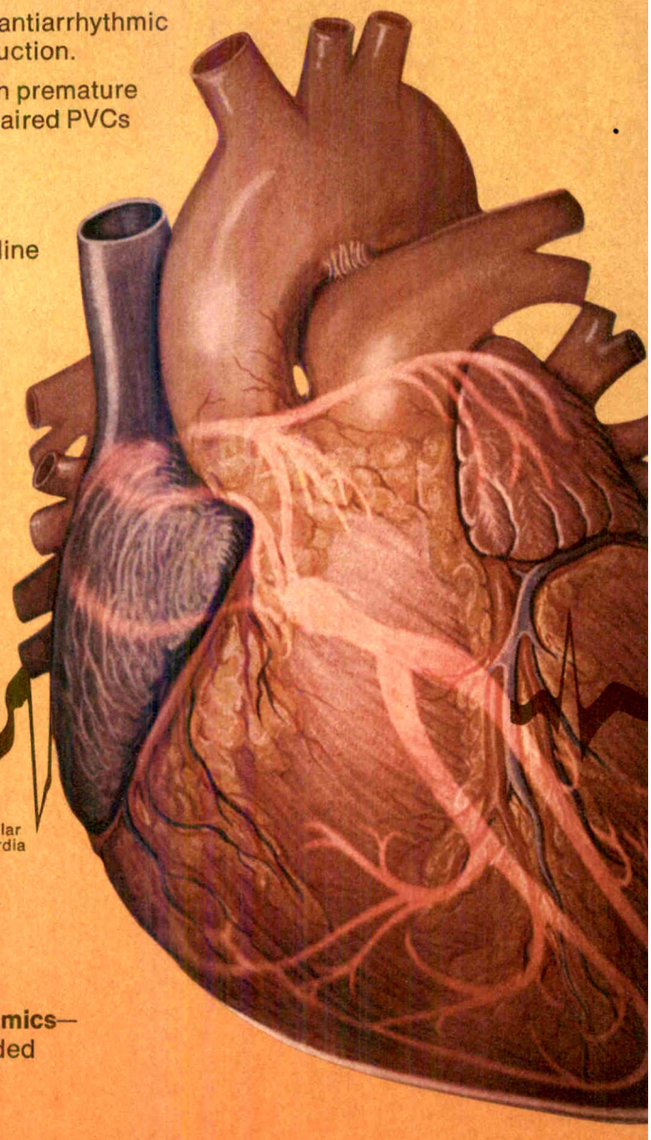

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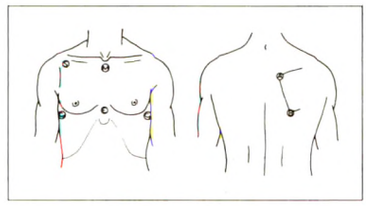

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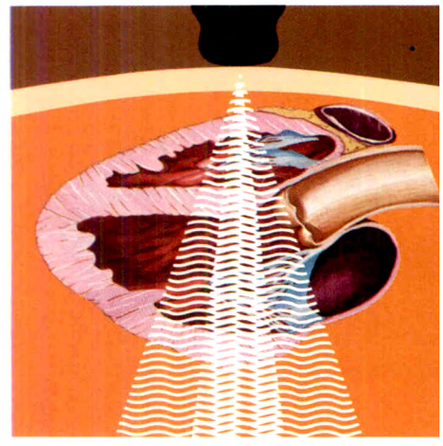

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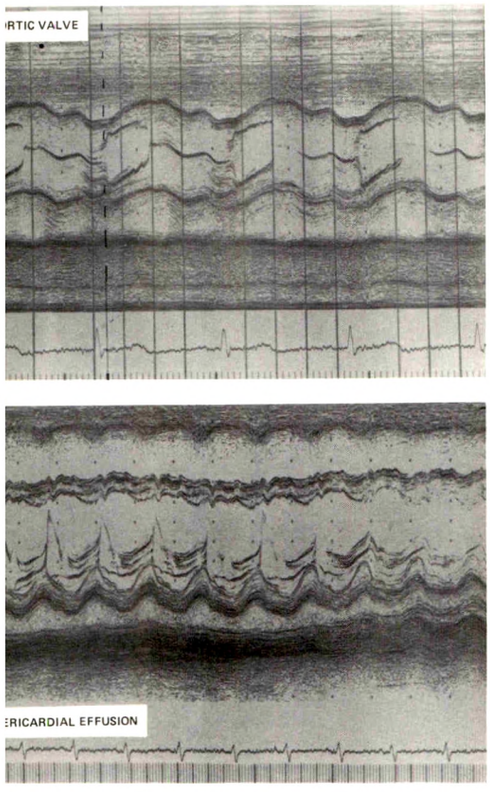

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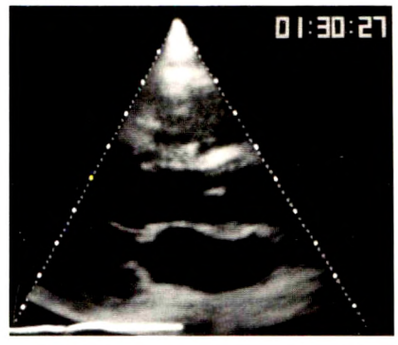

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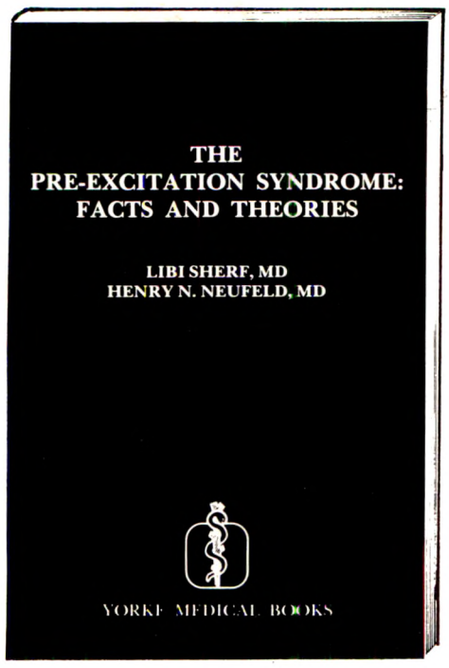

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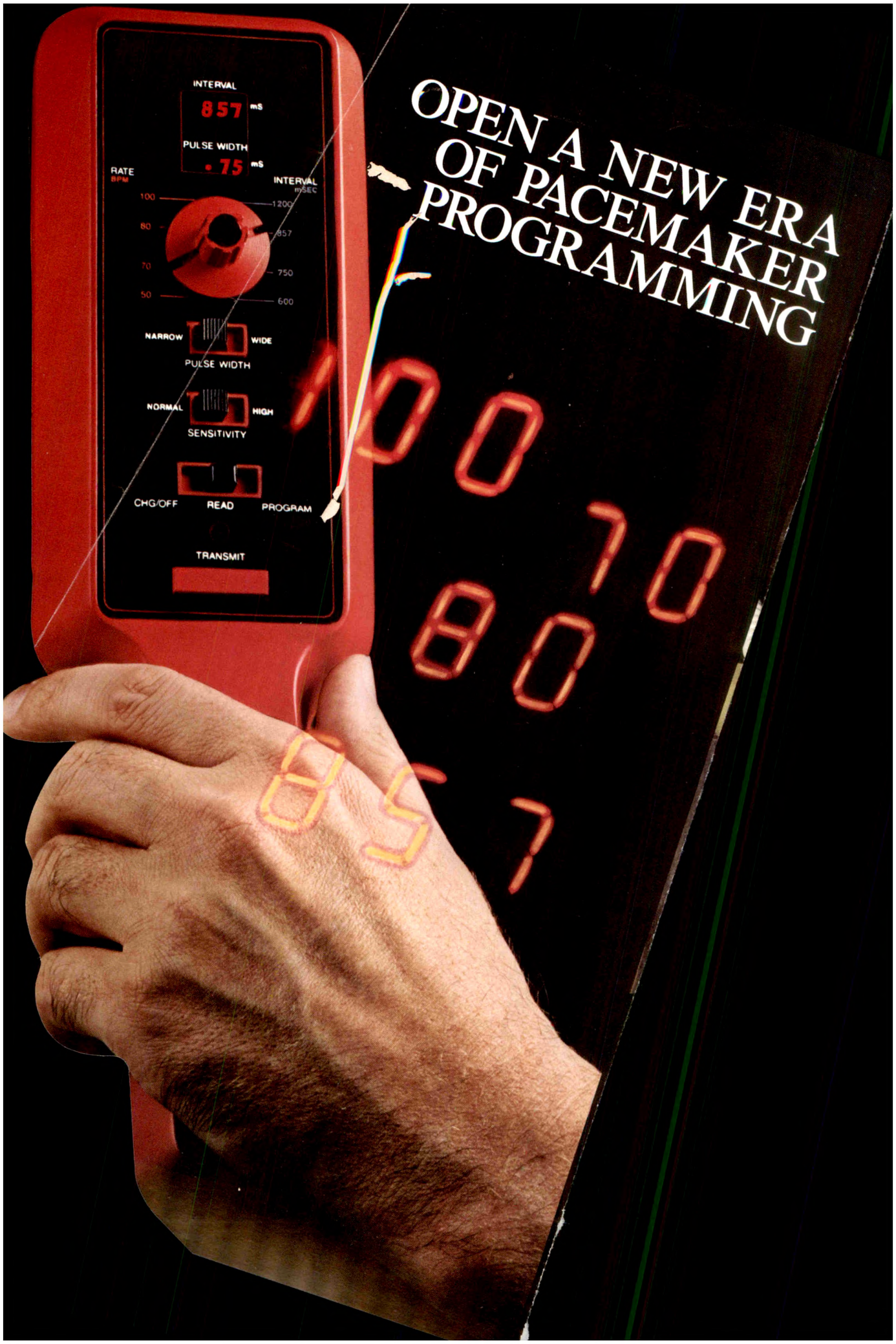
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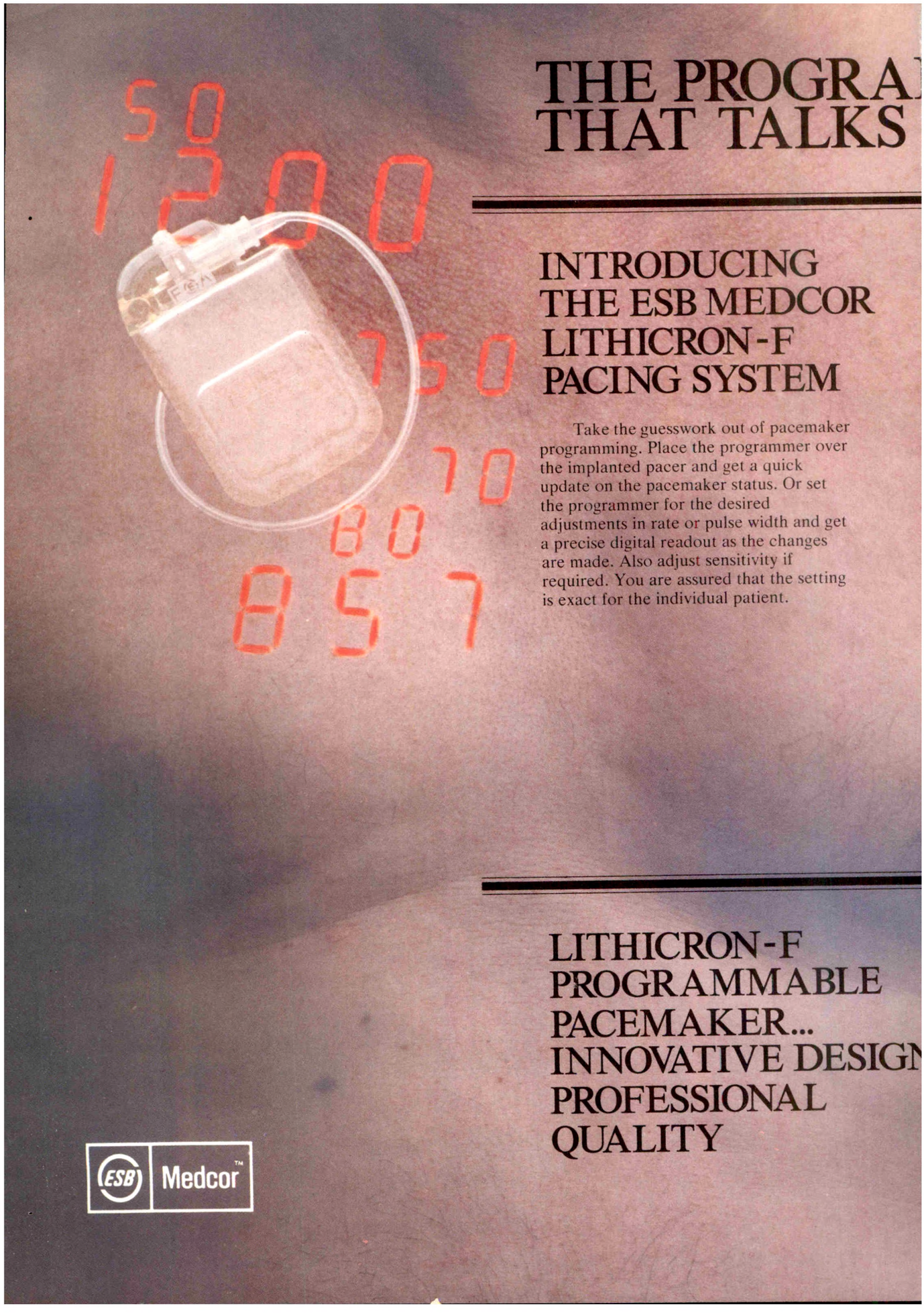

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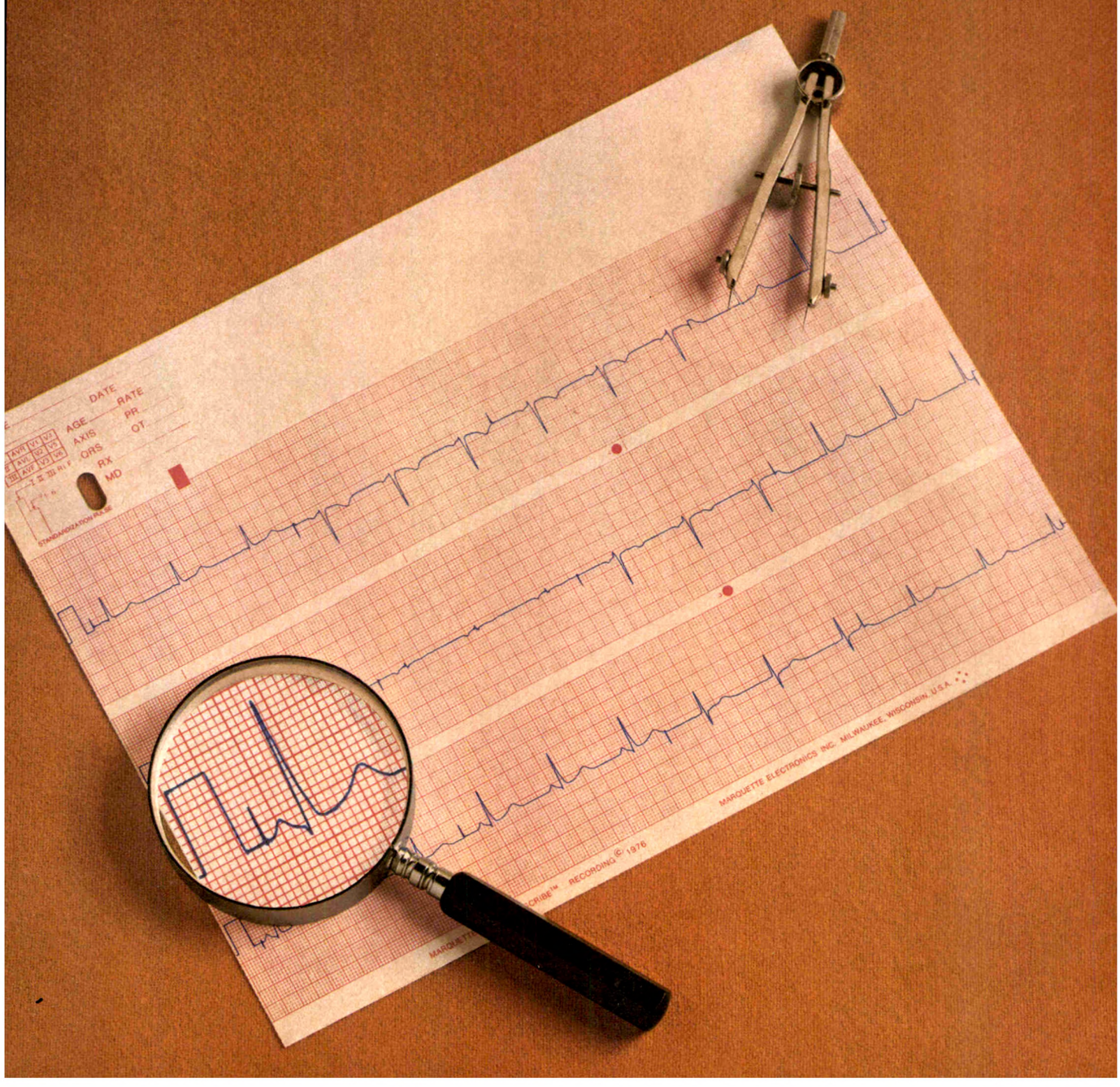

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Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hyponatremia may be caused or aggravated, especially when Aldactone is administered in combination with other diuretics. Transient elevation of BUN and/or mild acidosis may occur. Aldactone potentiates the effect of other diuretics or antihypertensive agents, particularly ganglionic blocking agents; therefore the dosage of such drugs should be reduced by at least 50 percent when adding Aldactone. Gynecomastia may develop and in rare instances some breast enlargement may persist. Vascular responsiveness to norepinephrine may be reduced.

Spironolactone may cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazard to the fetus. Breast feeding should be discontinued when Aldactone is being used.

Adverse Reactions: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established. Adverse reactions are usually reversible upon discontinuation of the drug.

Dosage and Administration

For primary hyperaldosteronism: 400 mg. daily for three to four weeks (long test), or for four days (short test). For preparation for surgery or for long-term maintenance therapy, 100 to 400 mg. daily.

For edema in adults: Initial daily dosage is 100 mg. in divided doses but may range from 25 to 200 mg. daily. If after five days an adequate diuretic response has not occurred, a second diuretic which acts more proximally in the renal tubule may be added. The dosage of Aldactone should remain unchanged when other diuretic therapy is added.

For edema in children: Initial daily dosage should provide approximately 1.5 mg. per pound of body weight (3.3 mg./kg.) in divided doses.

For essential hypertension: Initial adult daily dosage of 50 to 100 mg. in divided doses, alone or with diuretics which act more proximally in the renal tubule, or with other antihypertensive agents. Continue treatment for at least two weeks since maximal response may not occur before this time. Adjust subsequent dosage according to patient response.

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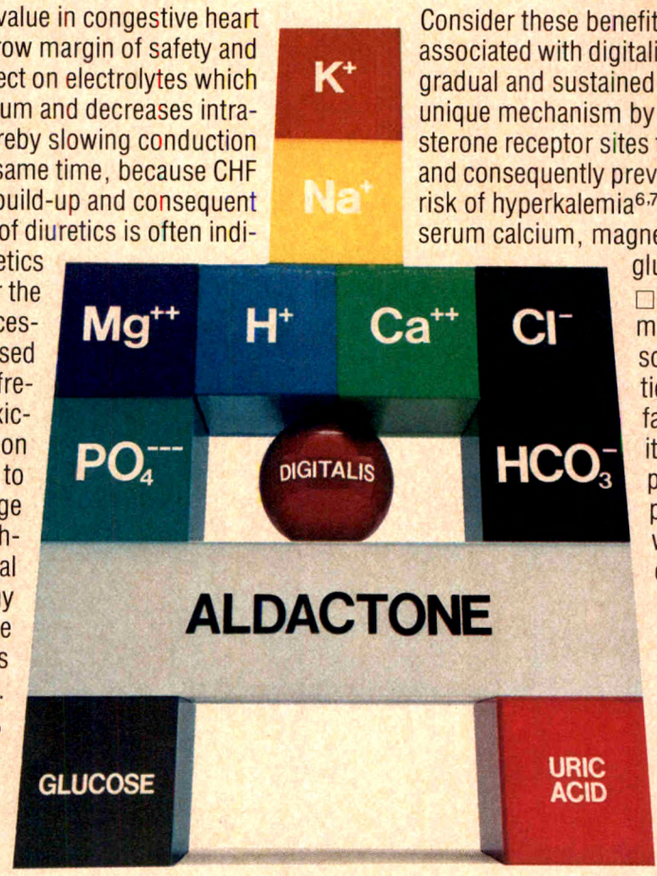

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□ Aldactone is indicated for management of edema and sodium retention in those patients with congestive heart failure who are taking digitalis, or in the treatment or prevention of hypokalemia in patients taking digitalis, when other measures are considered inadequate or inappropriate. □ When diuretic therapy is indicated, prescribe Aldactone to help preserve the delicate balance of electrolytes during digitalis therapy.

1. Kirkendall, W.M.: What's With Hypertension These Days? Consultant *11*:13-15 (Jan.) 1971.
2. Maronde, R.F.; Milgrom, M. and Dickey, J.M.: Potassium Loss with Thiazide Therapy, Am. Heart J. *78*:16-21 (July) 1969.
3. Cardiac Glycosides, Section 4, in Kastrup, E. K. (Editor): Facts and Comparisons, St. Louis, Facts and Comparisons, Inc., Jan. 1975, pp. 140-141C.
4. Weibert, R. T.: Heading Off Adverse Reactions. Thiazide Diuretics, Curr. Prescr. *3*:62-69 (Oct.) 1977.
5. Mudge, G. H., Diuretics and Other Agents Employed in the Mobilization of Edema Fluid, Chapter 39, in Goodman, L. S., and Gilman, A. (Editors): The Pharmacological Basis of Therapeutics, ed. 5., New York, Macmillan Publishing Co., Inc., 1975, pg. 836.
6. Laragh, J. H.: Diuretics in the Management of Congestive Heart Failure, Hosp. Pract. 5:43-50 (Nov.) 1970.
7. Tobian, L. J., Jr.: The Clinical Approach to Essential Hypertension, Hosp. Pract. *10*:33-44 (July) 1975.

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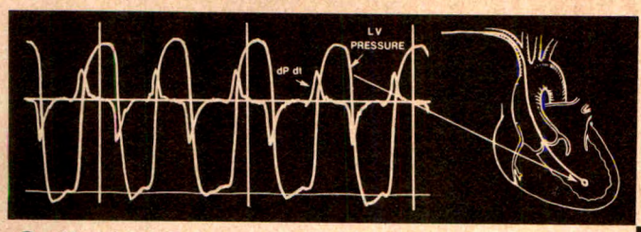

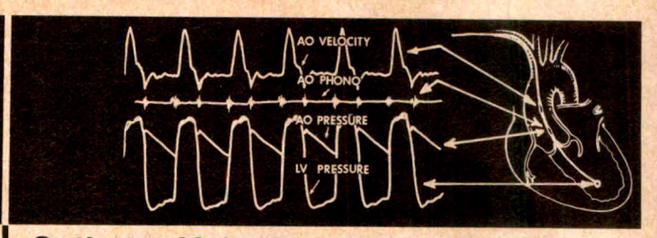

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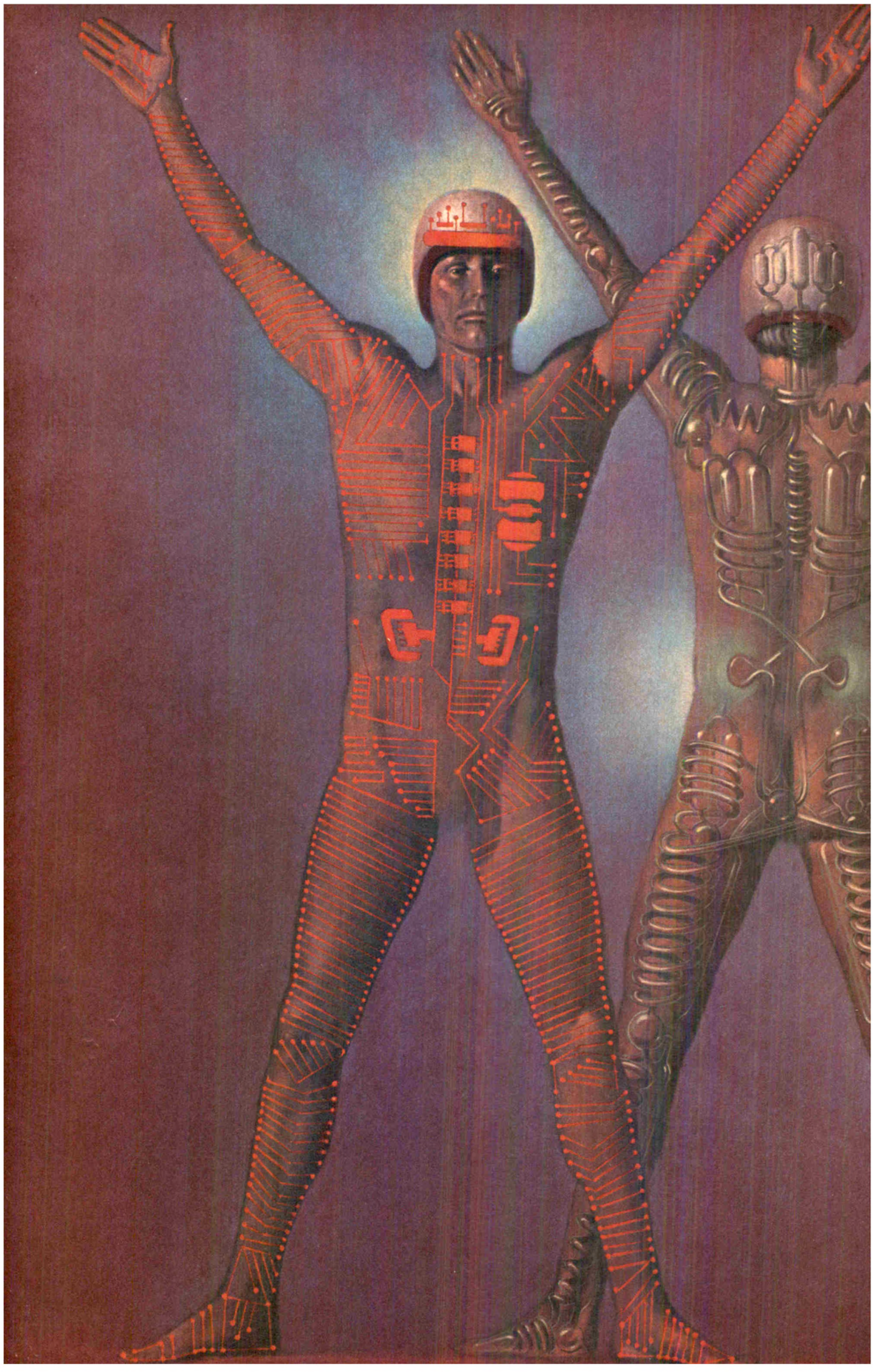

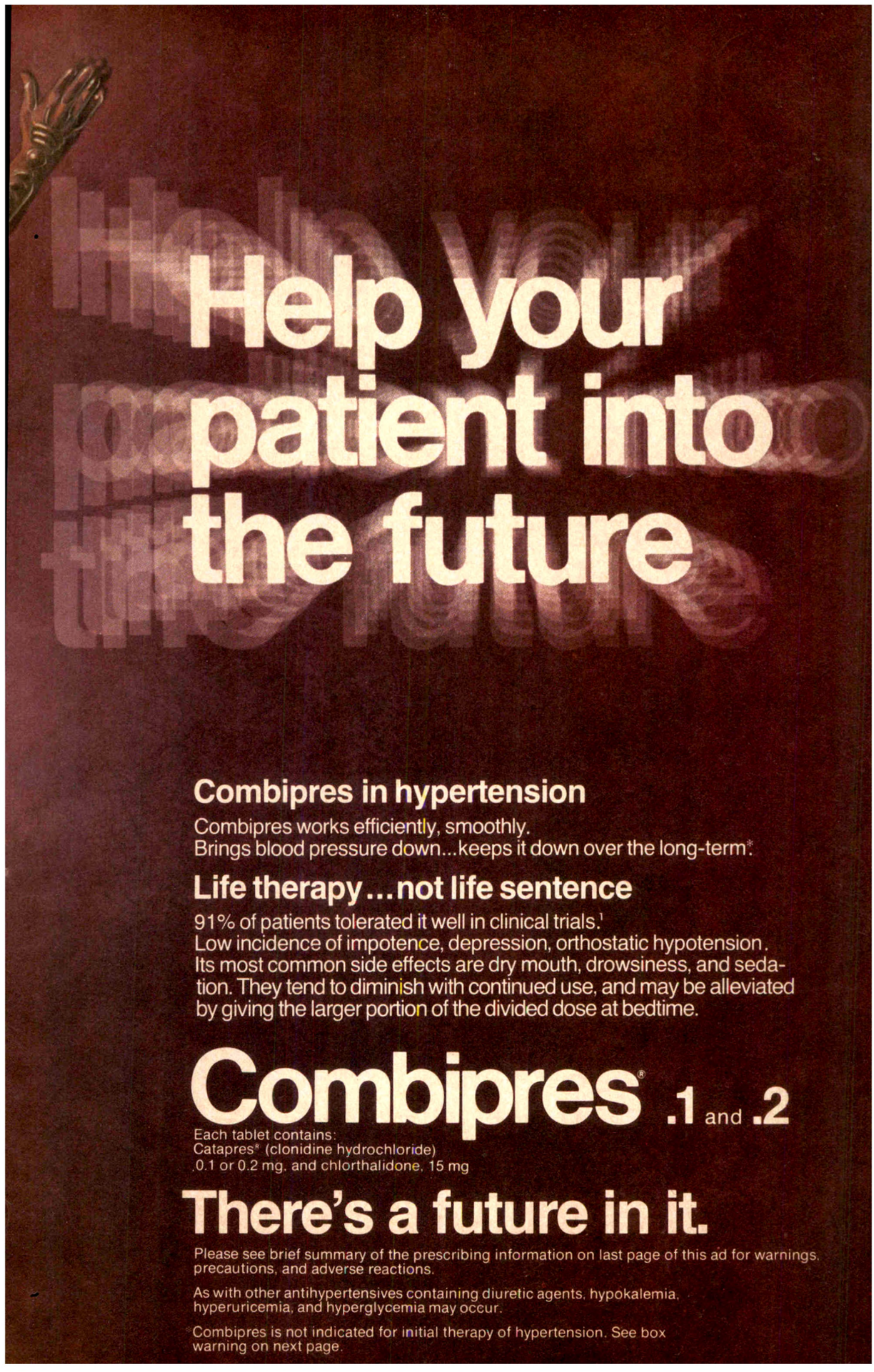
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Indication: The drug is indicated in the treatment of hypertension (see box warning).

Contraindications: Patients with known hypersensitivity to chlorthalidone and patients with severe renal or hepatic diseases.

Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

A decreased glucose tolerance evidenced by hyperglycemia and glycosuria may develop inconsistently. This condition, usually reversible on discontinuation of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed should be checked regularly.

As with other diuretic agents hypokalemia may occur (see Precautions). Hyperuricemia may be observed on occasion and acute attacks of gout have been precipitated. In cases where prolonged and significant elevation of blood uric acid concentration is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Idiosyncratic drug reactions such as aplastic anemia, thrombocytopenia, leukopenia, agranulocytosis, and necrotizing angiitis have occurred, but are rare.

The remote possibility of pancreatitis should be considered when epigastric pain or unexplained gastrointestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reported with this general class of compounds include: jaundice, xanthopsia, paresthesia and photosensitization.

Overdosage: *Catapres (clonidine hydrochloride):* Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

How Supplied: Combipres® 0.1 (Each tablet contains clonidine hydrochloride 0.1 mg + chlorthalidone,15 mg). It is available as pink, oval, single-scored compressed tablets in bottles of 100.

Combipres® 0.2 (Each tablet contains clonidine hydrochloride 0.2 mg + chlorthalidone,15 mg). It is available as blue, oval, single-scored compressed tablets in bottles of 100.

For complete details, please see full prescribing information.

1. Data on file at Boehringer Ingelheim Ltd.

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Precordial Mechanical Stimulation for Exposing Electrical Instability in the Ischemic Heart

BERNARD LOWN, MD, FACC
RICHARD L. VERRIER, PhD, FACC
CHARLES M. BLATT, MD*

Boston, Massachusetts

Sequential mechanical pulsing of the chest wall with three stimuli failed to induce arrhythmias in normal dogs. After coronary arterial occlusion, this technique evoked in 11 of 12 animals repetitive ventricular responses including ventricular fibrillation in 7 and ventricular tachycardia in 2. These responses corresponded closely to those elicited by electrical testing. In four conscious animals after recovery from myocardial infarction, precordial pulsing induced repetitive ventricular arrhythmias. The type of arrhythmia produced depended on the degree of prematurity of the third pulse in the sequence. The use of precordial mechanical stimulation can perhaps be modified and adapted as a method of detecting persons at high risk for sudden cardiac death.

Identifying the patient with ischemic heart disease at increased risk for sudden death depends on demonstration of advanced grades of ventricular premature beats.[1] But such extrasystoles are ubiquitous in patients with coronary heart disease, whereas some patients resuscitated from ventricular fibrillation exhibit no telltale ectopic activity. The ventricular premature beat, in addition to being an indirect marker of susceptibility to ventricular fibrillation, is random in occurrence, and advanced grades may not be reproducible in repeated monitoring sessions.[2] Furthermore, there is no certainty that any level of arrhythmia suppression will prove protective. Therefore, there is need for a noninvasive maneuver that will help expose the presence of electrical instability of the myocardium and thereby aid in identifying persons at risk of sudden death.

When a single stimulus is delivered to the ventricular myocardium, a single response is elicited. Electrical instability is presumed to be present when such a single pulse delivered early in the cardiac cycle is followed by multiple responses.[3,4] Exposure of electrical instability is facilitated by the delivery of three closely coupled sequential pulses.[5] In this study we examined whether external precordial mechanical stimulation of the chest wall in animals with acute and chronic myocardial ischemia can precipitate repetitive ventricular extrasystoles.

Materials and Methods

Experimental procedure: Sixteen healthy mongrel dogs of either sex weighing 10 to 20 kg were used. Five or more days before the study, the animals were intravenously anesthetized with alpha chloralose (100 mg/kg body weight) and subjected to thoracotomy performed through the fourth left intercostal space. An occlusive balloon catheter was placed around the left anterior descending coronary artery 2 to 3 mm distal to its origin. The inflation tube of the catheter was exteriorized through a subcutaneous tunnel in the nape of the neck.

On the day of study, the dogs were once again anesthetized with alpha chloralose. Ventilation was maintained by means of a cuffed endotracheal tube attached to a Harvard constant volume pump. Sufficient oxygen was admixed with room air to maintain arterial partial pressure of oxygen and pH in the physiologic range of 90 to 150 mm Hg and 7.35 to 7.45, respectively. Arterial blood pressure

From the Cardiovascular Research Laboratory, Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts. This study was supported in part by Grant MH-21384 from the National Institute of Mental Health, and by Grants HL-07776 and HL-18783 from the National Heart, Lung, and Blood Institute of the National Institutes of Health, Bethesda, Maryland. Manuscript received March 28, 1978; revised manuscript received May 15, 1978, accepted May 17, 1978.

* Medical Scientist Trainee Fellow at the College of Physicians and Surgeons, Columbia University, New York, New York, supported in part by Training Grant GM 02042 (Medical Scientist Training Grant) from the U.S. Public Health Service, Bethesda, Maryland.

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TABLE I
Maximal Ventricular Arrhythmia Induced With Precordial Mechanical Stimulation in 12 Anesthetized Dogs During Coronary Occlusion and Reperfusion

Arrhythmia	10 Minute Occlusion (no. of dogs)	Abrupt Reperfusion* (no. of dogs)
Ventricular fibrillation	7	4
Ventricular tachycardia	2	0
Repetitive extrasystole	2	0
None	1	4†

* In four animals that had ventricular fibrillation during testing with coronary occlusion, the balloon was prematurely released in order to effect resuscitation, therefore only eight dogs were available for study.

† In these four animals the balloon occluder released slowly because of malfunction.

was monitored by means of a large lumen catheter inserted in the femoral artery and connected to a Statham P23ID pressure transducer. The electrocardiogram was recorded from lead II and monitored continuously on an oscilloscope.

Mechanical precordial stimulation: Both a mechanical and an electrical means of cardiac testing were used to assess susceptibility to ventricular fibrillation. The electrical methods used have previously been described.[3,4] Mechanical testing of the heart was accomplished by delivering a quick thump to the chest with an industrial tacking device modified by attachment of a plunger with a hard rubber stopper on its tip. This mechanical pulser delivered approximately 0.25 joule, a value determined with use of a ballistic pendulum.* The trigger mechanism for the electrical solenoid was connected to a precision delay generator (1 percent accuracy) synchronized to the electrocardiographic R wave. One, two or three mechanical pulses could be delivered in rapid succession. An external plastic housing permitted firm positioning of the solenoid on the animal's chest. The thump was delivered in the region of the mid sternum while the dog was supine. The energy of the mechanical stimulator was at a setting just sufficient to induce a propagated ventricular response in mid diastole. The pulse was delivered thereafter progressively earlier in the cardiac cycle, in 5 msec steps, until ventricular depolarization was no longer obtained. This point defined the boundary of the effective refractory period for the mechanical stimulus. The delay of the first mechanical pulse (P_1) was then set 10 msec beyond the effective refractory period. The delay of the second (P_2) and third (P_3) pulses was similarly determined. The three mechanical pulses resulted in a sequence of three early extrasystoles.

Protocol: *In 12 dogs,* the left anterior descending coronary artery was then occluded for 10 minutes by inflating the previously implanted balloon catheter. During coronary occlusion three sequential mechanical pulses were delivered at 1 minute intervals. At 10 minutes the balloon catheter was abruptly deflated, and sequential mechanical pulsing was immediately initiated. When ventricular fibrillation emerged it was terminated within 3 to 5 seconds by a direct-current capacitor discharge delivered through copper paddles (100 cm^2) that had previously been applied across the thorax. A rest period of 20 minutes was allowed after each occlusion trial.

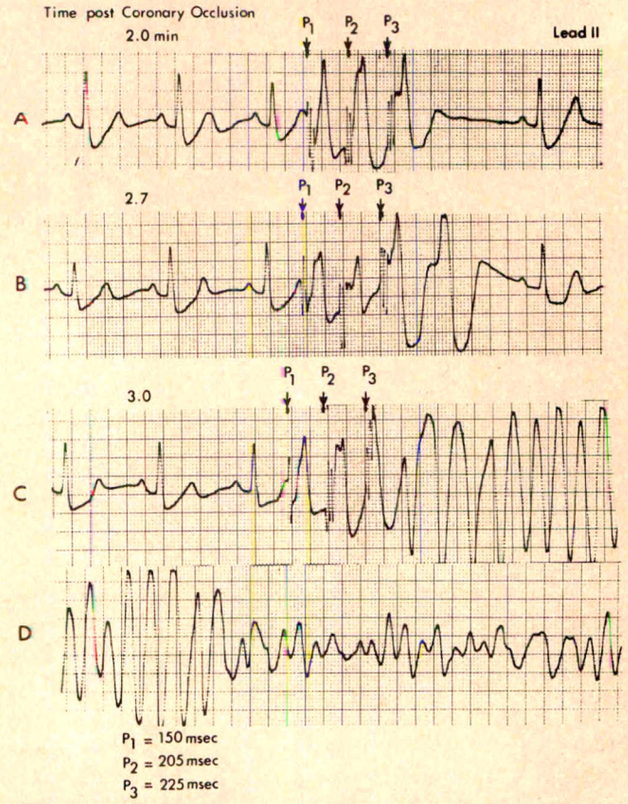

FIGURE 1. A, 2 minutes after coronary occlusion, three closely timed sequential mechanical stimuli (P_1, P_2, P_3) evoke three propagated responses. **B,** within 2.7 minutes a repetitive extrasystole is induced. **C** and **D,** after 3 minutes of occlusion precordial mechanical pulsing induces ventricular fibrillation.

In 6 of these 12 dogs, a repeat coronary occlusion was performed, and changes in vulnerability were assessed electrically with use of the sequential pulsing technique. Electrical stimulation was accomplished using a bipolar catheter (Medtronic no. 5819) inserted through a jugular vein and positioned in the apex of the right ventricle under fluoroscopic control. This catheter was present only during electrical testing. Three sequential pulses were delivered 10 msec beyond the boundary of the effective refractory period (determined by a stimulus of twice threshold intensity) of each preceding beat. To determine the fibrillation threshold, the current of the third pulse was increased by 4 milliampere (ma) steps until ventricular fibrillation occurred. The minimal current for inducing ventricular fibrillation defined the ventricular fibrillation threshold.

Four dogs underwent permanent coronary occlusion and were allowed to recover from anesthesia. Electrocardiograms were thereafter monitored using a telemetry system connected to an automated direct printout. Tracings were obtained at hourly intervals. Ventricular tachycardia occurred in all animals 3 to 12 hours after permanent coronary occlusion and spontaneously terminated within 48 hours. These dogs were then studied in the conscious state within 12 hours of cessation of arrhythmia. Mechanical stimuli were then delivered to the left lateral thorax at the point of maximal cardiac impulse while the dogs were gently restrained in the standing position. The response to a single stimulus was tested first. If ventricular tachycardia was elicited with a single stimulus, no further

* The energy output of the mechanical pulser was determined using a ballistic pendulum energy measurement as follows: (1) H = D sin (1/2 $\sin^{-1}$ D/L), where D = measured horizontal deflection, H = calculated height and L = length of string suspending pendulum. (2) E = Mass × H, where E = peak potential energy. A mass of 10,250 g was deflected by the thumper a horizontal distance, D, of 10.75 cm. Therefore, E = 2,510 g-cm = 0.246 joule. The mechanical pulser and the QRS synchronizing electronic devices were developed by Mr. Nicholas Jordan.

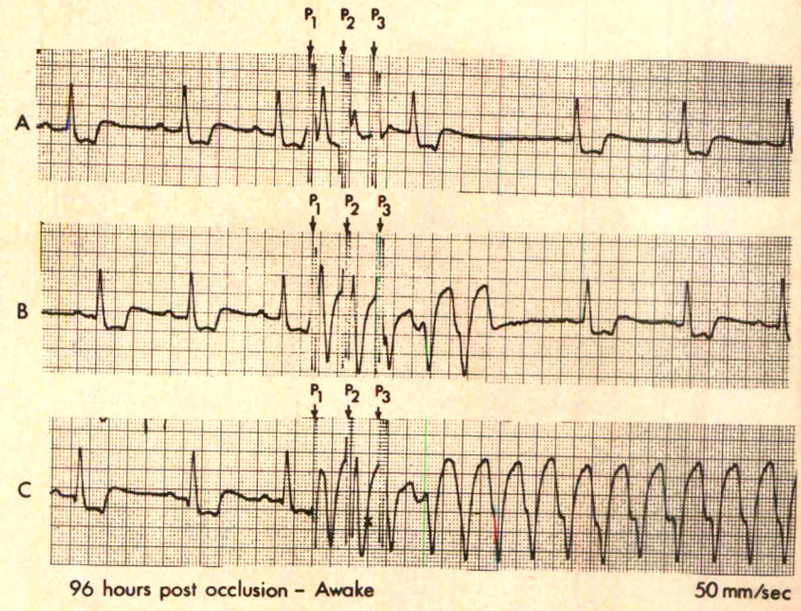

FIGURE 2. In a conscious animal 96 hours after coronary occlusion, three sequential precordial mechanical stimuli evoke a repetitive extrasystole (**A**), two extrasystoles (**B**) and, finally, ventricular tachycardia that persists (**C**). The increased grade of arrhythmia results from shortening the cycle of the third precordial pulse, P_3.

stimuli were applied. If ventricular tachycardia was not induced using a single stimulus, two and then three stimuli were delivered. The last stimulus in the sequence was delivered progressively earlier in diastole in 5 msec steps as described. These animals were studied daily until arrhythmia could no longer be induced by three sequential mechanical stimuli.

Results

Transient coronary occlusion: Before coronary occlusion, neither ventricular fibrillation nor ventricular tachycardia was induced by sequential mechanical pulsing. However, after obstruction to coronary flow, mechanical stimulation of the chest wall evoked in 11 of 12 animals repetitive ventricular arrhythmias, including ventricular fibrillation in 7, ventricular tachycardia in 2 and repetitive extrasystoles in 2 (Table I, Fig. 1). Arrhythmias could be elicited 2 to 6 minutes after coronary occlusion. After 10 minutes, upon release of occlusion, mechanical pulsing induced ventricular fibrillation in four of eight animals. This generally occurred within 5 to 20 seconds after abrupt reperfusion. In one dog spontaneous ventricular fibrillation occurred during occlusion. In all other animals fibrillation was directly precipitated by electrical or mechanical stimulation.

The time course for exposure of susceptibility to ventricular fibrillation by means of mechanical pulsing ran closely parallel to that obtained by electrical testing. In six dogs, before occlusion, a stimulus intensity greater than 30 ma was required to induce ventricular fibrillation. Within 2 to 4 minutes after coronary occlusion, ventricular fibrillation was precipitated by a stimulus of 2 ma. Six to 8 minutes after occlusion the fibrillation threshold returned to the preocclusion level. Immediately after release of occlusion, ventricular fibrillation could be evoked for several seconds by a 2 ma stimulus.

Permanent coronary occlusion: Precordial mechanical stimulation was performed in four conscious dogs recovering from myocardial infarction. Within 24 hours of the spontaneous cessation of ventricular tachycardia, delivery of a single precordial mechanical pulse during the vulnerable period reinduced ventricular tachycardia in all animals. On the following day, three pulses were required to evoke ventricular tachycardia in three of the dogs. In the remaining animal a single thump still elicited the arrhythmia (Table II, Fig. 2). In no animal was ventricular fibrillation induced. Three days after spontaneous termination of the ventricular tachycardia, mechanical stimulation with one, two or three sequential pulses no longer provoked ventricular arrhythmia.

TABLE II
Maximal Ventricular Arrhythmia Induced With Precordial Mechanical Stimulation in Four Conscious Dogs During Recovery Phase After Myocardial Infarction

Dog no.	Hours After Coronary Occlusion			
	48	72	96	120
1	NT	VT	VT	RE
2	VT	VT	VT	0
3	VT	NT	0	0
4	VT	0	0	0

NT = not tested; RE = repetitive extrasystole; VT = ventricular tachycardia; 0 = arrhythmia not provoked.

Discussion

It has long been known that touch or pressure applied to the living heart can evoke a propagated response. This is a common experience in the cardiac catheterization laboratory. The earliest experiments comparing the effects of mechanical and electrical stimulation on cardiac excitability were carried out by Brooks et al.[6] Using a plastic rod with a tapered round tip, they applied a quick mechanical thrust directly to the exposed myocardium. To effect both thrust and prompt withdrawal, the rod was attached to the moving core of a

solenoid. The mechanical stimulus could be delivered at any desired interval in the cardiac cycle. Results were identical with the two testing methods. Using a single mechanical stimulus, these workers were unable to demonstrate any phase of the cycle during which they could reproducibly provoke either repetitive firing or fibrillation.

Cardiac response to mechanical stimulation: Mechanical precordial thumping has been shown to be effective in terminating ventricular fibrillation if applied immediately after the onset of fibrillation,[7] and the procedure has become standard practice in cardiopulmonary resuscitation. The basis for the effectiveness of the mechanical stimulus is that it depolarizes myocardial fibers by transduction of the mechanical pulse into an electrical depolarization.[8] The heart responds as a mechanoelectrical transducer. Pressure-induced extrasystoles are a familiar result of manipulating intracardiac catheters. The transducer element of a mechanoreceptor undergoes change in conduction with stretch. Teorell[9] suggested that this phenomenon is due to a coupling between membrane potential and hydrostatic pressure difference across the cell membrane due to changes in electro-osmotic permeability (namely, deformation of membrane structure subjects a cell to volume displacement). With expulsion of solution, the cell shrinks. This alters the concentration gradient of ions within membrane pores, thereby changing electrical conductance with resulting alteration in transmembrane potential. Recently, Zoll et al.[10] introduced a mechanical stapler for achieving mechanical thumping of the chest wall and showed that in some men ventricular premature beats can be evoked with this technique. Cohn et al.[11] utilized chest thumping in man to induce postextrasystolic potentiation during echocardiography. Blatt et al.[12] found that precordial mechanical stimulation can be used to assess the degree of digitalization.

Effect of sequential mechanical stimulation during myocardial ischemia: We have now demonstrated that by programming three sequential precordial mechanical pulses in the animal with myocardial ischemia, one can elicit repetitive electrical activity. In the normal as well as in the infarcted heart, single pulses greatly above threshold are required to trigger ventricular fibrillation when delivered during the brief interval of the ventricular vulnerable period. However, when three early sequential pulses are administered, the current required for ventricular fibrillation is markedly reduced and, in the animal with infarction, currents at threshold level for diastolic depolarization suffice to precipitate ventricular fibrillation.[3] The time course of change in vulnerability to ventricular fibrillation during coronary occlusion and release demonstrated by mechanical pulsing is identical to that observed with electrical stimulation of the endocardium. Of special importance is the finding that in the awake animal precordial mechanical pulsing exposes the presence of electrical instability after sustained coronary occlusion and development of myocardial infarction. The time course is similar to that found using invasive electrical methods during the postrecovery stage of myocardial infarction.[13]

Clinical implications: In the acutely ischemic canine heart, immediately after coronary occlusion, a repetitive ventricular response can be elicited with a single threshold stimulus delivered in early diastole but outside the ventricular vulnerable period.[14] Employing the repetitive ventricular response phenomenon in man, Green et al.[15] demonstrated that the technique permits identification of patients at increased risk of having malignant arrhythmias. It thus may not be necessary to utilize multiple repetitive pulses in man to expose the presence of electrical instability. Because currently available drugs to prevent ventricular fibrillation exact a significant cost in adverse reactions, there has been little justification for treating the large number of patients with ischemic heart disease in the hope of saving the minority likely to die suddenly. It is thus essential to identify those patients predisposed to malignant ventricular arrhythmias. Adapting the technique of precordial mechanical stimulation to elicit a single repetitive ventricular response may afford a method of detecting these patients.

References

1. **Lown B, Wolf M:** Approaches to sudden death from coronary heart disease. Circulation 44:130–142, 1971
2. **Calvert A, Lown B, Gorlin R:** Ventricular premature beats and anatomically defined coronary heart disease. Am J Cardiol 39: 890–902, 1977
3. **Axelrod PJ, Verrier RL, Lown B:** Vulnerability to ventricular fibrillation during acute coronary arterial occlusion and release. Am J Cardiol 36:776–782, 1975
4. **Matta RJ, Verrier RL, Lown B:** The repetitive extrasystole as an index of vulnerability to ventricular fibrillation. Am J Physiol 230:1461–1466, 1976
5. **Thompson P, Lown B:** Sequential R/T pacing to expose electrical instability in the ischemic ventricle (abstr). Clin Res 20:401, 1972
6. **Brooks CMcC, Gilbert JL, Suckling EE:** Excitable cycle of the heart as determined by mechanical stimuli. Proc Soc Exp Biol Med 117:634–637, 1964
7. **Pennington JE, Taylor J, Lown B:** Chest thump for reverting ventricular tachycardia. N Engl J Med 283:1192–1195, 1970
8. **Lown B, Taylor J:** Editorial on "thump-version." N Engl J Med 283:1223, 1970
9. **Teorell T:** Electrokinetic considerations of mechanoelectrical transduction. Ann NY Acad Sci 137:950–966, 1966
10. **Zoll PM, Belgard AH, Weintraub MJ, et al:** External mechanical cardiac stimulation. N Engl J Med 294:1274–1275, 1976
11. **Cohn PF, Angoff GH, Zoll PM, et al:** A new, noninvasive technique for inducing post-extrasystolic potentiation during echocardiography. Circulation 56:598–605, 1977
12. **Blatt CM, Lown B, Rabinowitz SH:** A noninvasive means for assessing glycoside toxicity: Mechanically induced repetitive ventricular response. Proc Soc Exp Biol Med 156:531–533, 1977
13. **Wolff GA, Veith F, Lown B:** A vulnerable period for ventricular tachycardia following myocardial infarction. Cardiovasc Res 2: 111–121, 1968
14. **Jenzer H, Lohrbauer L, Lown B:** Response to single threshold stimuli following acute myocardial infarction. Proc Soc Exp Biol Med 141:606–608, 1972
15. **Green HL, Reid PR, Schaeffer AH:** The repetitive ventricular response in man: an index of ventricular electrical instability (abstr). Am J Cardiol 41:400, 1978

Progressive Transmural Electrographic, Myocardial Potassium Ion/Sodium Ion Ratio and Ultrastructural Changes As a Function of Time After Acute Coronary Occlusion

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The progressive transmural electrographic, biochemical and ultrastructural changes as a function of time after acute coronary occlusion were systematically assessed in eight dogs. Transmural plunge electrodes with poles 1 mm apart were placed in the ischemic and nonischemic zones, and coronary occlusion was maintained for 4 hours. Transmural full thickness biopsy specimens were obtained from each zone for electron microscopy before, and 1 and 4 hours after occlusion. Endocardial and epicardial layers were also obtained for assessment of myocardial potassium ion (K^+) and sodium ion (Na^+) concentrations. Before coronary occlusion, local Q waves were recorded an average depth of 1.0 ± 0.34 mm from the endocardial surface. After 1 hour of occlusion, Q waves appeared at an average depth of 3.8 ± 0.67 mm and progressed to a depth of 5.2 ± 0.7 mm at 2 hours, 6.2 ± 0.5 mm at 3 hours and 7.0 ± 0.5 mm at 4 hours. After 1 hour, ultrastructural changes of early ischemia, including a decrease in glycogen and mild mitochondrial swelling, were seen in the endocardial layer; the epicardial layer showed normal morphologic features. After 4 hours, the endocardial layer showed well developed ischemic changes marked by the loss of mitochondrial cristae, vacuolization, the appearance of amorphous mitochondrial densities, an increase in interfibrillary space and the appearance of I bands. In contrast, the epicardial layer at this time showed only early ischemic changes. At the end of 4 hours, the endocardial layer showed a marked decrease in myocardial K^+ concentration and an increase in Na^+ concentration leading to complete reversal of the K^+/Na^+ ratio (0.7 ± 1.0; $P < 0.001$). In the epicardial layer, a smaller decrease in K^+ concentration and an increase in Na^+ concentration occurred, resulting in a diminution but not a reversal of the K^+/Na^+ ratio (1.4 ± 0.2; $P < 0.005$).

Thus, the dynamic evolution of an acute myocardial infarction involves a sequential progression from endocardium to epicardium as a function of time, resulting in an epicardial "border zone" in the early stages after acute coronary occlusion.

Considerable recent interest has focused on the determination and reduction of infarct size.[1] Central to these studies is the concept that after acute coronary occlusion there is a portion of severely ischemic myocardium that is delicately balanced between irreversible injury or necrosis and survival. To date, most studies have examined the affected left ventricular myocardial areas using experimental means such as local electrograms, length and tension gauges as well as serial myocardial enzyme determinations.[2–8] The data measured reflect the *sum* of transmural events. However, little is known of the temporal sequence of abnormalities that occur within the affected left ventricular zone from endocardium to epicardium. This study was undertaken to determine

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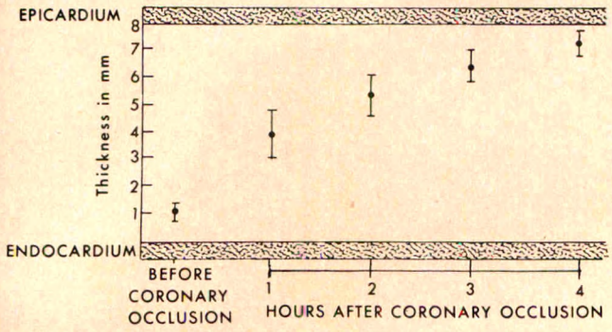

FIGURE 1. Progression of intramyocardial Q waves from endocardial to epicardial layers during 4 hours of coronary occlusion (mean value ± standard error of the mean).

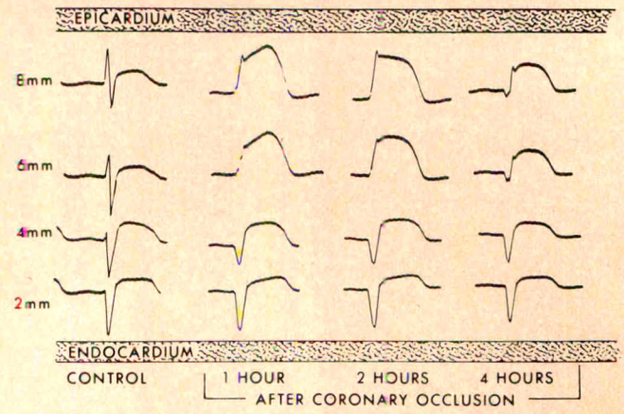

FIGURE 2. A typical experiment demonstrating the progression of intramyocardial Q waves from endocardium to epicardium. Before coronary occlusion, only a small initial R wave is present in the endocardial 2 mm electrogram but the more superficial electrograms (4, 6 and 8 mm) show significantly taller R waves. After 1 hour of coronary occlusion, Q waves appear in both the 2 mm and 4 mm electrograms, forming a QS complex. At 2 hours of coronary occlusion, the 2 and 4 mm electrograms show a QS complex, but another small Q wave also appears in the 6 mm electrogram. After 4 hours of coronary occlusion, both the 6 and 8 mm electrograms show significant Q waves, thus completing the transmural spread of Q waves from endocardium to epicardium.

the progressive transmural electrographic, biochemical and ultrastructural changes as a function of time after acute coronary occlusion for 1 to 4 hours.

Methods

Experimental procedure: Studies were performed in eight dogs weighing 25 to 30 kg, anesthetized with intravenous sodium pentobarbital (30 mg/kg) and ventilated with a Harvard respirator. The heart was exposed through a mid sternal incision and supported in a pericardial cradle. A polyethylene tube was introduced through an external jugular vein for intravenous infusion. Central aortic pressure was monitored using a Statham P23Db transducer and a wide bore, stiff catheter introduced through the right common carotid artery. The left anterior descending coronary artery was isolated 2 to 3 cm distal to its origin. Potentially ischemic and nonischemic zones were demarcated using epicardial electrograms after transient coronary occlusion.[3,4] The central ischemic zone was characterized by marked S-T elevation, the border zone by S-T depression and T wave inversion and the nonischemic zone by an essentially unchanged epicardial electrogram.[3,4] After the transient occlusion was released, at least a 10 minute period was allowed for the electrograms to revert to normal.

Intramyocardial electrograms and biopsy: Three 18 gauge plunge needle electrodes, each containing eight terminals located 1 mm apart, were inserted, two in the potentially ischemic (1 cm apart) and one in the nonischemic zone for obtaining intramyocardial electrograms.[9] A ten minute period was allowed for injury potentials to return to normal after insertion of the needle electrodes into the myocardium. Unipolar intramyocardial electrograms (0.1 to 100 hertz) were

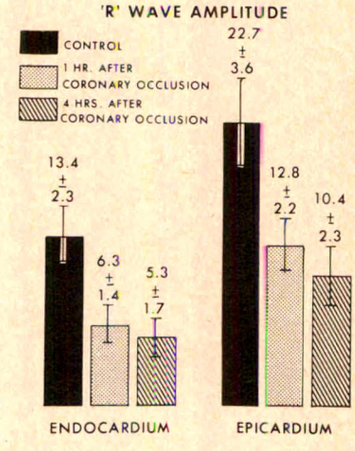

FIGURE 3. Progression of intramyocardial R wave amplitude (in mv) in the endocardial and epicardial layers during 4 hours of coronary occlusion.

TABLE I

Myocardial Potassium Ion (K^+) and Sodium Ion (Na^+) Concentration After 4 Hours of Coronary Occlusion (mean values ± standard error of the mean)

	Nonischemic Zone			Ischemic Zone		
	K^+	Na^+	K/Na Ratio	K^+	Na^+	K/Na Ratio
Endocardial layer	6.2 ± 0.3	3.0 ± 0.1	2.1 ± 0.1	3.5 ± 0.3	5 0 ± 0.3	0.7* ± 0.1
Epicardial layer	6.2 ± 0.4	3.2 ± 0.4	2.0 ± 0.1	5.7 ± 0.4	4.2 ± 0.4	1.4† ± 0.2

* $P < 0.001$.
† $P < 0.005$.

FIGURE 4. Photomicrograph from the nonischemic zone showing normal morphologic features. The myofibrils are compact and unswollen. There is an abundance of cell glycogen. The mitochondria have a dense matrix, small nonspecific dense granules and uniform tightly packed cristae. (×17,100, reduced by 15 percent.)

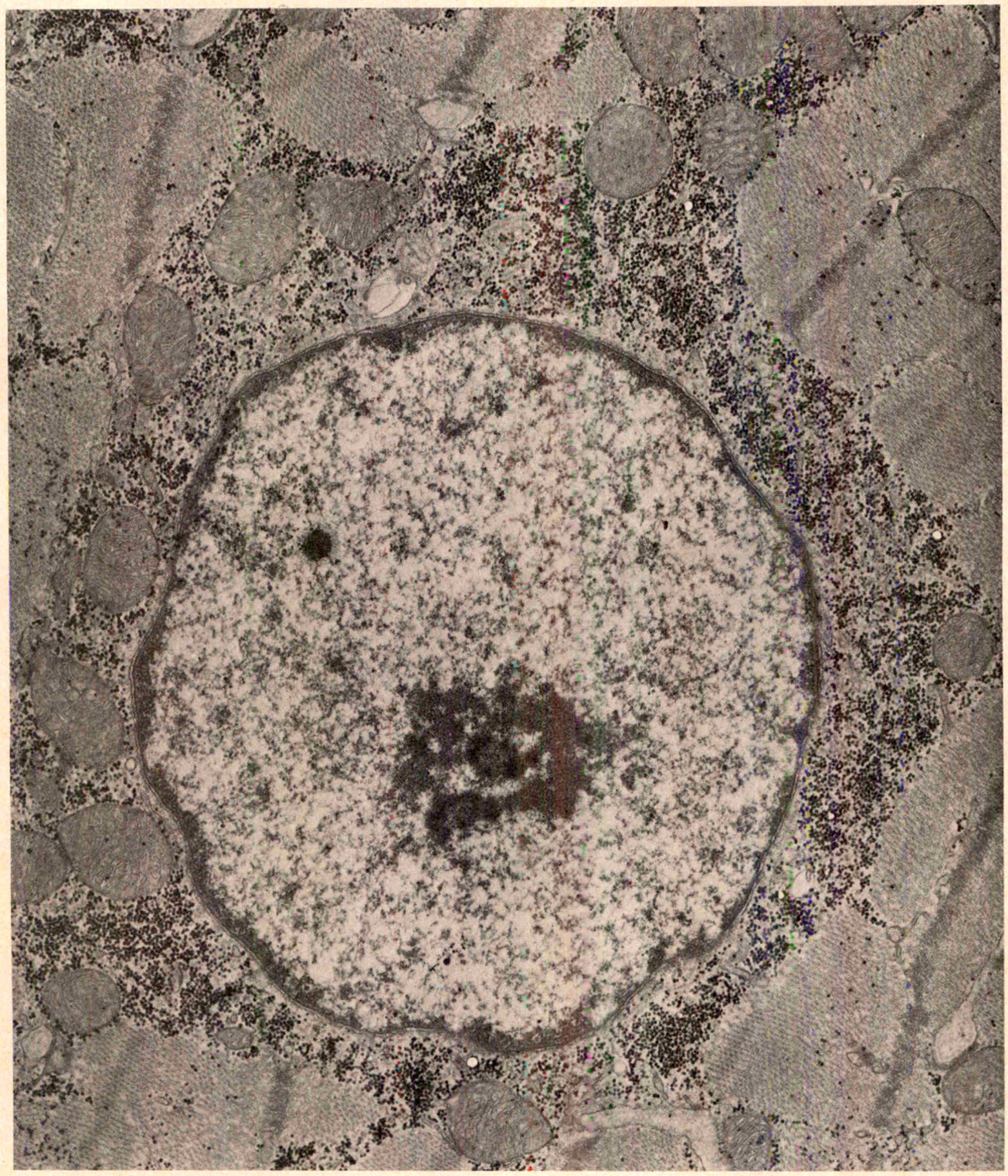

FIGURE 5. Photomicrograph from the nonischemic zone showing nuclear morphologic features. The nuclear chromatin is uniform and unclumped. The nucleolus is seen in the center of the nucleus, which is surrounded by abundant tightly packed glycogen granules. (×30,000, reduced by 15 percent.)

FIGURE 6. Photomicrograph of tissue from the nonischemic zone demonstrating normal capillary morphologic features with compact and uniform endothelium. (×30,000, reduced by 13 percent.)

recorded using a switchbox connected to an Electronics for Medicine multichannel oscilloscopic recorder. After control electrographic recordings were taken, a full thickness punch biopsy was performed from both the potentially ischemic and nonischemic zones within 1 cm of the plunge electrode using a punch sucker technique and avoiding blood vessels.[10,11] This biopsy technique utilizes a 14 gauge needle with a square keenly sharpened tip connected to an aspiration suction line with a Likens tube interposed and a sponge covering the outflow arm of the collecting tube. The method avoids undue compression, trauma or distortion.[10,11]

After the control electrograms and myocardial biopsies were performed, the left anterior descending coronary artery was ligated for 4 hours. Electrographic recordings were obtained at 5 minute intervals for the first 15 minutes and at 15 minute intervals thereafter. At the end of 1 hour, another punch bi-

FIGURE 7. Photomicrograph showing early or slight ischemic changes in the endocardial layer of the ischemic zone after 1 hour of coronary occlusion. There is a slight increase in the interfibrillary spaces and a *mild decrease* in cell glycogen. Slight mitochondrial swelling with no amorphous matrix densities is seen. The fibers are contracted, and no I bands are seen. (×30,000, reduced by 13 percent.)

opsy was performed from the ischemic zone within 1 cm of the plunge electrode.

Myocardial specimens for Na^+ and K^+ concentrations and histology: After 4 hours of coronary occlusion, the dogs were sacrificed and 1 to 1.5 cm^3 full thickness blocks of myocardium obtained from the central ischemic and nonischemic zones. These myocardial blocks were then divided into three parts—the endocardial, middle and epicardial thirds. The specimens were trimmed of all fat and extraneous tissue and homogenized to determine their sodium and potassium concentrations by emission flame photometry.[5] In addition, a third full thickness myocardial specimen was also obtained for histologic evaluation from both the ischemic and nonischemic zones at this time.

Intramyocardial electrograms were analyzed for transmural location, appearance and spread of local unipolar Q waves

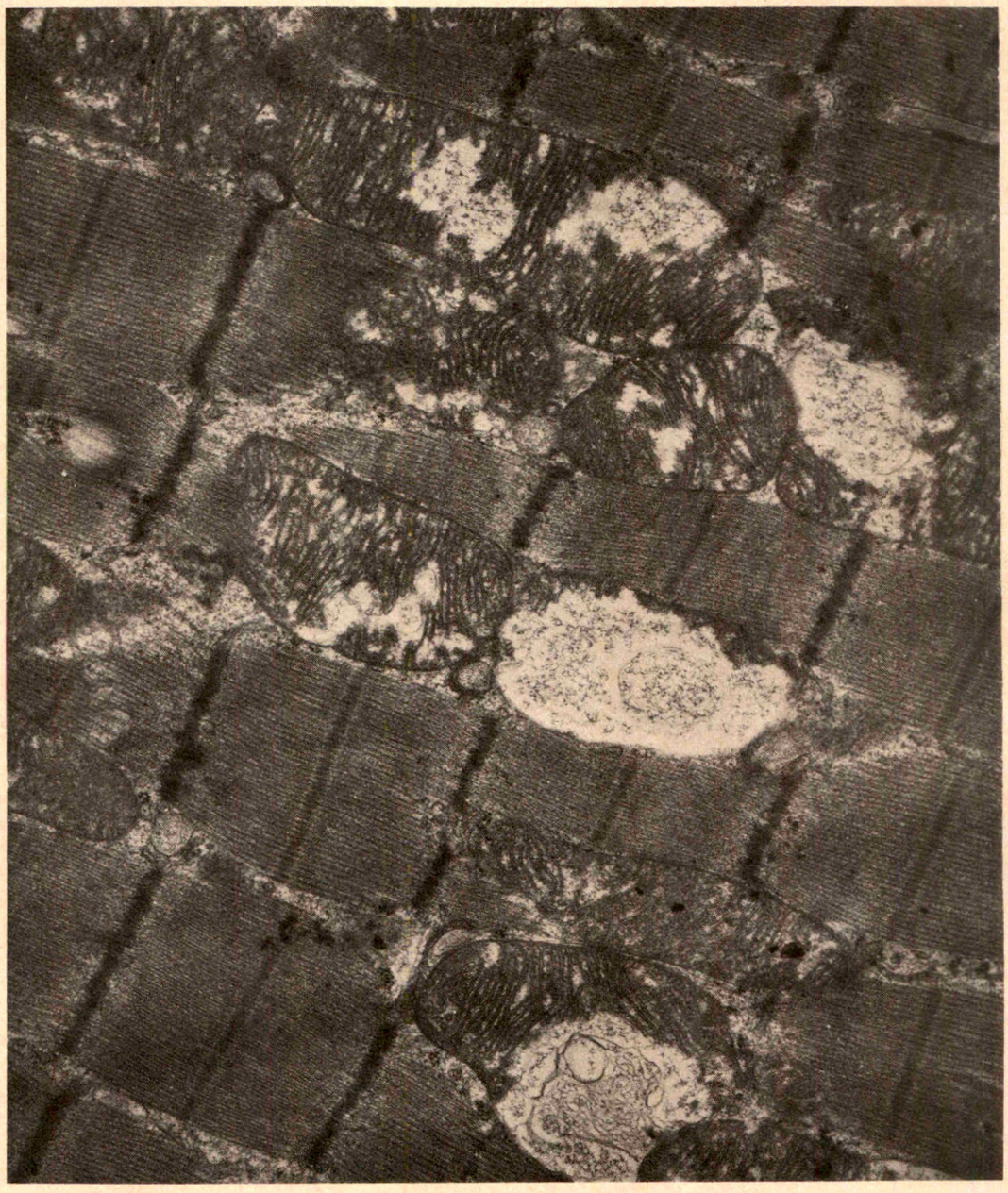

FIGURE 8. Photomicrograph of tissue from the endocardial layer of the ischemic zone after 1 hour of coronary occlusion. A significant loss of glycogen, a mild increase in interfibrillary space and mitochondrial swelling are evident. The fibers are contracted and no I bands are visualized. (×30,000 reduced by 23 percent.)

(>0.03 second) as well as R wave amplitude. The myocardial tissues obtained for histologic examination were fixed in glutaraldehyde. Thin polychrome sections were examined for light microscopy and ultrathin sections for electron microscopy. The changes in the electron microscopic samples were classified as: (1) normal; (2) early or slight ischemic changes; and (3) later or well developed ischemic changes similar to the classification of Kloner et al.[12] The transmural location of these changes was also observed. The emission flame photometry results for myocardial sodium and potassium concentrations were tabulated for endocardial and epicardial layers and the K^+/Na^+ ratio determined for each layer in the ischemic and nonischemic zones.[5]

Results

Progression of intramyocardial Q waves: Before coronary occlusion, the transmural electrograms revealed Q waves only in the endocardial layer at an average depth of 1.0 ± 0.34 mm (range 0 to 3 mm). After coronary occlusion, Q waves appeared progressively from endocardium to epicardium as a function of time during the 4 hours of occlusion (Fig. 1). After 1 hour of occlusion, Q waves were visualized at a depth of 3.8 ± 0.67 mm from the endocardial surface, progressing to a depth of 5.2 ± 0.7 mm 2 hours, 6.2 ± 0.5 mm 3 hours and 7.0 ± 0.5 mm 4 hours after coronary occlusion. Figure 2 shows a typical experiment demonstrating the progression of intramyocardial Q waves.

Progression of R wave amplitude: After coronary ligation, the R wave amplitude decreased significantly in both the endocardial and epicardial electrograms (Fig. 3). Before coronary occlusion, the R wave amplitude was 13.4 ± 2.3 mv in the endocardial third and 22.7 ± 3.6 mv in the epicardial third. However, after 1 hour of coronary occlusion, the endocardial R wave amplitude decreased to 6.3 ± 1.4 mv (P <0.02) and after 4 hours to 5.3 ± 1.7 mv. In the epicardial third, the R wave amplitude decreased to 12.8 ± 2.2 mv within 1 hour after occlusion (P <0.001) and to 10.4 ± 2.3 mv after 4 hours. No differences in the progressively diminishing R wave amplitude were demonstrable between the endocardial and epicardial layers.

Myocardial potassium/sodium ratio: The myocardial potassium ion (K^+) and sodium ion (Na^+) concentrations of the endocardial and epicardial layers of both the nonischemic and ischemic zones are shown in Table I. In the nonischemic zone, the potassium and sodium concentrations of the endocardial and epicardial layers remained normal with respective K^+/Na^+ ratios of 2.1 ± 0.1 and 2.0 ± 0.1. In the ischemic zone, there was a marked decrease in potassium concentration and an increase in sodium concentration of the endocardial layer with a resultant reversal of the K^+/Na^+ ratio to 0.7 ± 0.1 (Table I). In the epicardial layer, however, a smaller decrease in potassium concentration and increase in sodium concentration occurred resulting in a diminution (and not a reversal) of the K^+/Na^+ ratio to 1.4 ± 0.2.

Morphologic appearances: Histologic examination of the biopsy material obtained before coronary occlusion from the potentially ischemic and nonischemic zones showed normal morphology of the endocardial and epicardial layers under light and electron microscopy (Fig. 4 to 6). The nuclear chromatin was uniform and unclumped. The myocardial fibers and fibrils were compact and unswollen. Cell glycogen was abundant. The mitochondria had a dense matrix, small nonspecific dense granules and uniform tightly packed cristae. There was no mitochondrial vacuolization. The capillary endothelium was compact, uniform and unswollen. The sarcoplasmic reticulum was unswollen and the myofibrils were usually contracted.

After 1 hour of coronary occlusion, the endocardial layer from the ischemic zone showed early or slight ischemic changes (Fig. 7 and 8). The nuclear chromatin was uniform and unclumped. There was no significant fiber swelling, but a slight increase in interfibrillary space could be seen. The cell glycogen was slightly decreased. Slight mitochondrial swelling was observed, but there were no amorphous mitochondrial matrix densities. The fibers remained contracted, and usually no I bands were seen. The epicardial layer showed normal morphologic features (Fig. 9).

After 4 hours of coronary occlusion, the endocardial layers showed well developed ischemic changes (Fig. 10 to 12). The nuclear chromatin showed clumping and margination. There was obvious fiber swelling with an increase in the interfibrillary space. There was marked mitochrondrial swelling with rarification of matrix density. Multiple amorphous matrix densities within the mitochondria were common, and occasionally vacuolization was observed. The muscle was usually relaxed, and prominent I bands were present. Significant capillary endothelial swelling was observed. The epicardial layers showed only early ischemic changes after 4 hours of coronary occlusion (Fig. 13 and 14).

Discussion

Disparity in severity of ischemic changes between subendocardial and epicardial myocardial layers: This study demonstrates that the dynamic process of an acute "transmural" myocardial infarction involves a sequential progression from endocardium to epicardium as a function of time after acute coronary occlusion. After 1 hour of coronary occlusion, local electrographic Q waves are seen only in the endocardial layers, whereas the epicardial layers show tall R waves. Concomitant histopathologic changes of early ischemia on electron microscopy are also seen only in the endocardial layers at this time; the epicardial layers show normal morphologic features. In contrast, after 4 hours of coronary occlusion, the Q waves have spread transmurally being visualized in both endocardial and epicardial layers. However, the endocardial layers show changes of severe ischemia on electron microscopy, whereas the epicardial layers still show early ischemic changes.

The change in R wave amplitude between 1 and 4 hours was not statistically significant; the major difference occurred within 1 hour. After 1 hour, although a slight further increase in R wave amplitude was noted,

FIGURE 9. Photomicrograph showing normal morphologic features of the epicardial layer of the ischemic zone after 1 hour of coronary occlusion. (×30,000, reduced by 15 percent.)

initial Q waves developed in most of the QRS complexes, resulting in QS or QR complexes. Further decreases in R wave amplitude measurement are generally not possible because a QS or QR configuration has developed.

The disparity in the severity of ischemic changes between the endocardial and epicardial layers is also manifested by the K^+/Na^+ concentration ratios of the epicardial and endocardial tissues at the end of 4 hours of coronary occlusion. The endocardial layers showed a marked decrease in potassium concentration and increase in sodium concentration causing reversal of K^+/Na^+ ratio, but the changes in epicardial layers were less marked, resulting in a decrease but not a reversal of the K^+/Na^+ ratio. Thus, at any given period after coronary occlusion within 4 hours, the degree of epicardial ischemic injury is considerably less than that in the endocardial layer. These findings are consistent with those of Rivas et al.,[13] who showed that epicardial blood flow was greater than endocardial flow after coronary

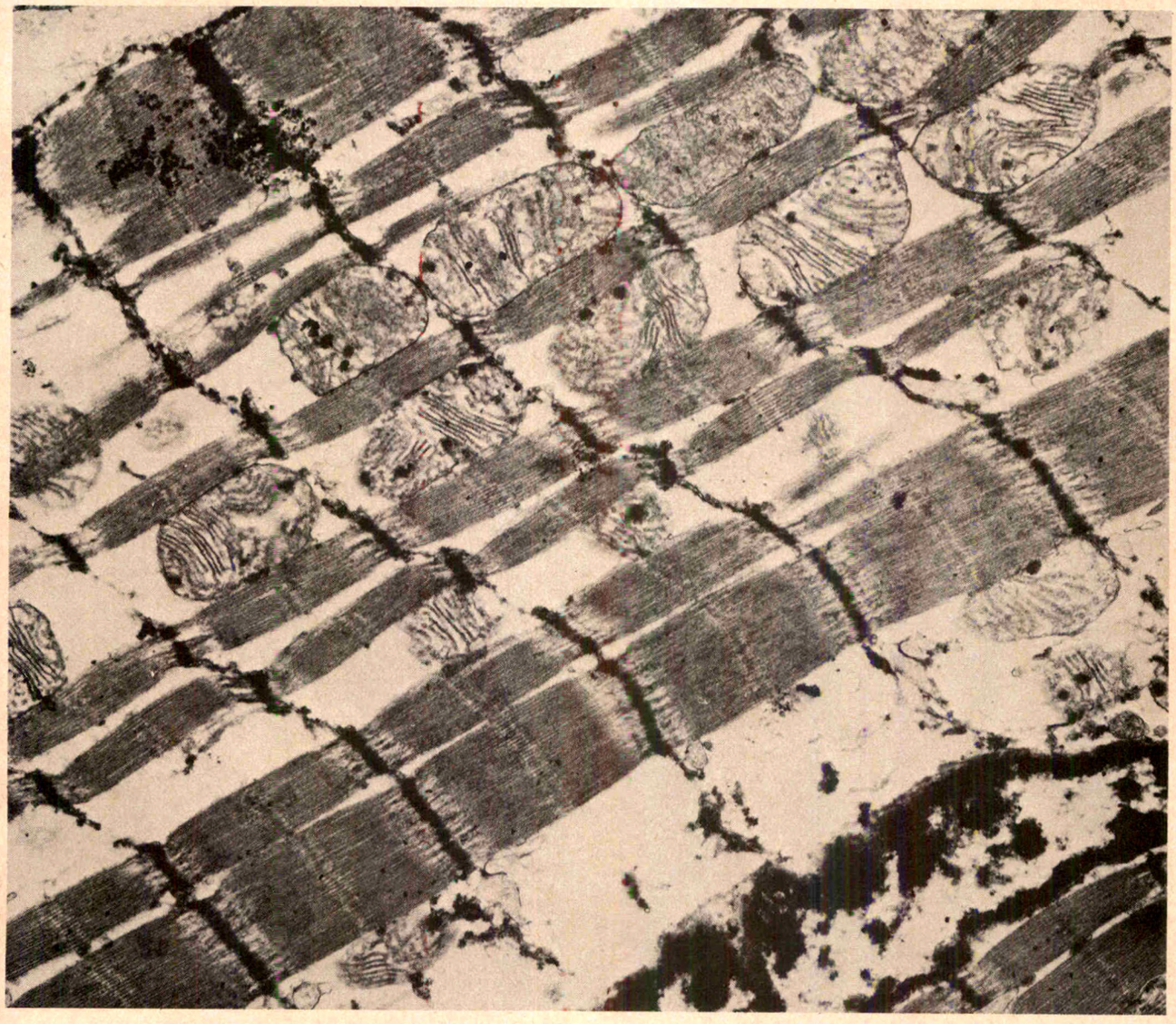

FIGURE 10. Photomicrograph showing well developed ischemic changes in the endocardial layer of the ischemic zone after 4 hours of coronary occlusion. Cell glycogen has completely disappeared. The myofibrils are swollen with a marked increase in interfibrillary spaces, and there is marked mitochondrial swelling with rarifaction of matrix density. Multiple amorphous bodies within the mitochondria and vacuolization are present. The muscle is relaxed, and prominent I bands are seen. In addition, margination and clumping of nuclear chromatin are evident **(lower right)**. (X30,000, reduced by 22 percent).

occlusion and that at necropsy the endocardium demonstrates a greater extent of infarction than the epicardial region.

Our observations are also consistent with those of Jennings et al.[14] and Reimer et al.,[15] who demonstrated that brief periods of coronary occlusion (20 to 40 minutes) result in subendocardial necrosis and that salvageable myocardium does exist in the subepicardial region. However, when the period of coronary occlusion is prolonged to 60 minutes, the percent of necrotic myocardium increases significantly. A recent histopathologic study by Reimer et al.[16] on the effects of coronary occlusion and reperfusion as a function of time indicates that, at 40 minutes of coronary occlusion,

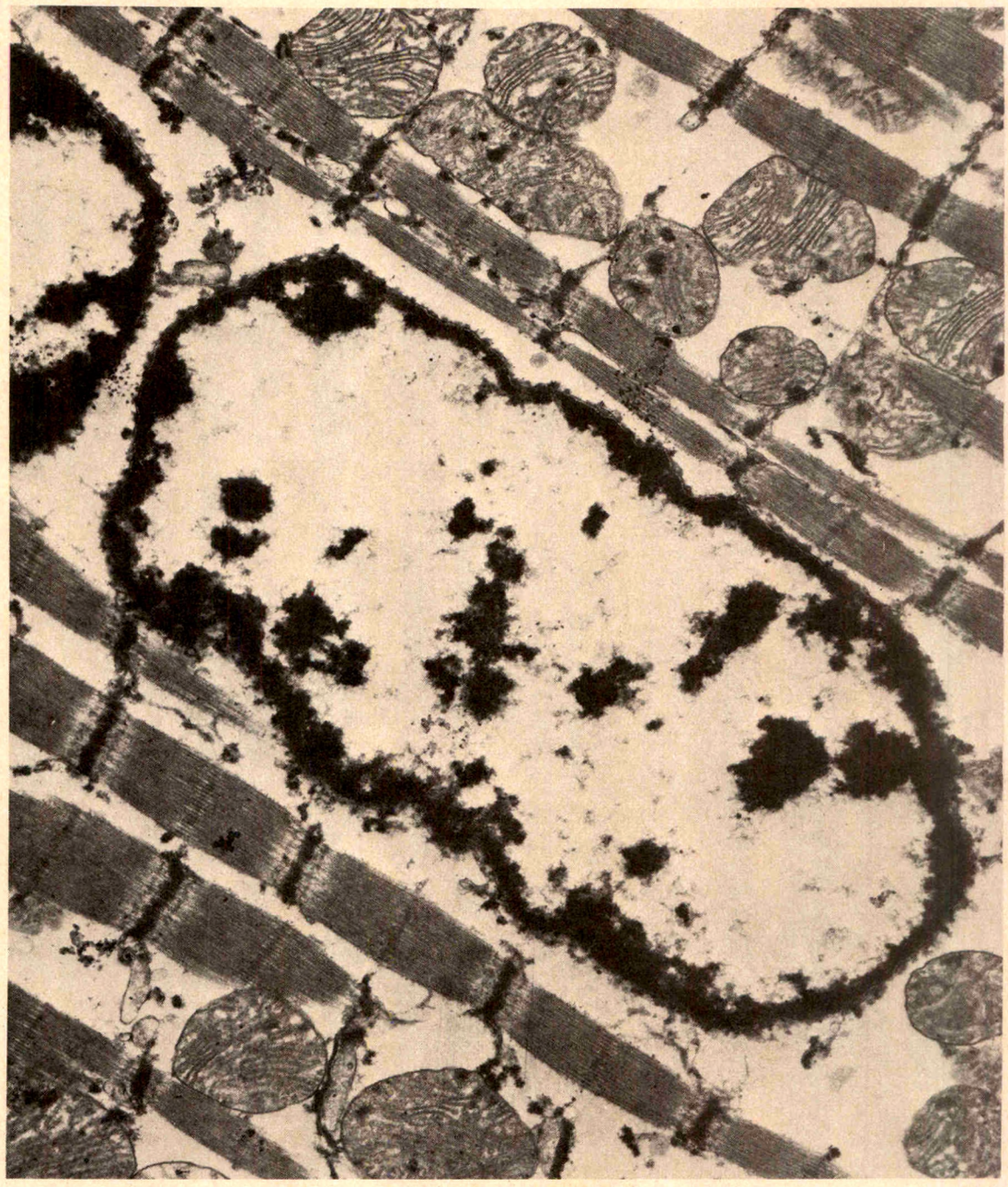

FIGURE 11. Photomicrograph showing nuclear morphologic features in the endocardial layer of the ischemic zone after 4 hours of coronary occlusion. Marked clumping and margination of nuclear chromatin are evident. (X30,000, reduced by 22 percent.)

myocyte necrosis occurs in the subendocardial region and progresses as a wave front toward the subepicardium. These observations were based on accumulation of data in different groups of dogs undergoing coronary occlusion for various time periods. In our study, myocardial biopsy specimens from the same animal during 4 hours of coronary occlusion were obtained and the progression in ultrastructural changes after 1 and 4 hours of coronary occlusion was observed in each experiment. The progression in ultrastructural changes was concomitant with electrographic progression of Q waves and abnormalities in myocardial potassium and sodium ratios.

Possible limitations of study: Because myocardial ischemic injury and infarction may not be homogeneous, the methodology of our study is limited by the performance of myocardial sampling with a biopsy technique 1 hour after occlusion. The tissue obtained after 4 hours of coronary occlusion was clearly more uniform because much larger blocks of muscle could then be obtained for histopathologic and biochemical analysis. Similarly, because the sampled myocardium was obtained from areas adjacent to but not precisely from the electrographic sites, it is possible that this difference affected our data. Despite these methodologic limitations of sampling, the consistency of the measurements evaluated within each experiment and between experiments strongly support the validity of the results obtained.

FIGURE 12. Photomicrograph showing intramyocardial capillary morphologic features in the endocardial layer after 4 hours of coronary occlusion. Marked swelling of the capillary endothelium is seen. (×30,000, reduced by 22 percent.)

Clinical implications: Our findings may have important potential implications in the context of the current widespread interest in determining and attempting to reduce the size of a myocardial infarct. It is generally recognized that after an acute coronary occlusion, the central zone of ischemic injury is surrounded by a partially ischemic zone, the so-called twilight or border zone. Previous studies[17,18] evaluating the central zone as a transmural entity have indicated that after 1 hour of coronary occlusion, the resultant abnormalities are irreversible whereas the surrounding border zone remains viable for a longer period. However, our data strongly suggest that the process of infarction within the central zone is nonhomogeneous and that in the early stages after acute coronary occlusion, the epicardial layer of the central zone exhibits electrographic,

FIGURE 13. Photomicrograph showing only early or slight ischemic changes in the epicardial layer of the ischemic zone after 4 hours of coronary occlusion. In contrast to Figure 10, cell glycogen is still present, and the myofibrils are less swollen and the increase in interfibrillary space is less marked. The mitochondria show slight swelling without vacuolization or appearance of amorphous bodies. There are no I bands. (×30,000, reduced by 22 percent.)

electron microscopic and biochemical characteristics of a true border zone. It is thus conceivable that viable and salvageable myocardium may exist within this layer of the central zone as well as in the surrounding border zone. The extent of this salvageable area may depend on the time elapsed after the coronary occlusion, myocardial oxygen requirements and the availability of accessory blood supply. To elucidate fully the potential of various interventions to salvage jeopardized myocardium, the study of infarct size and methods to reduce it must therefore evaluate the border zones that both surround and are included in the central affected area.

Acknowledgment

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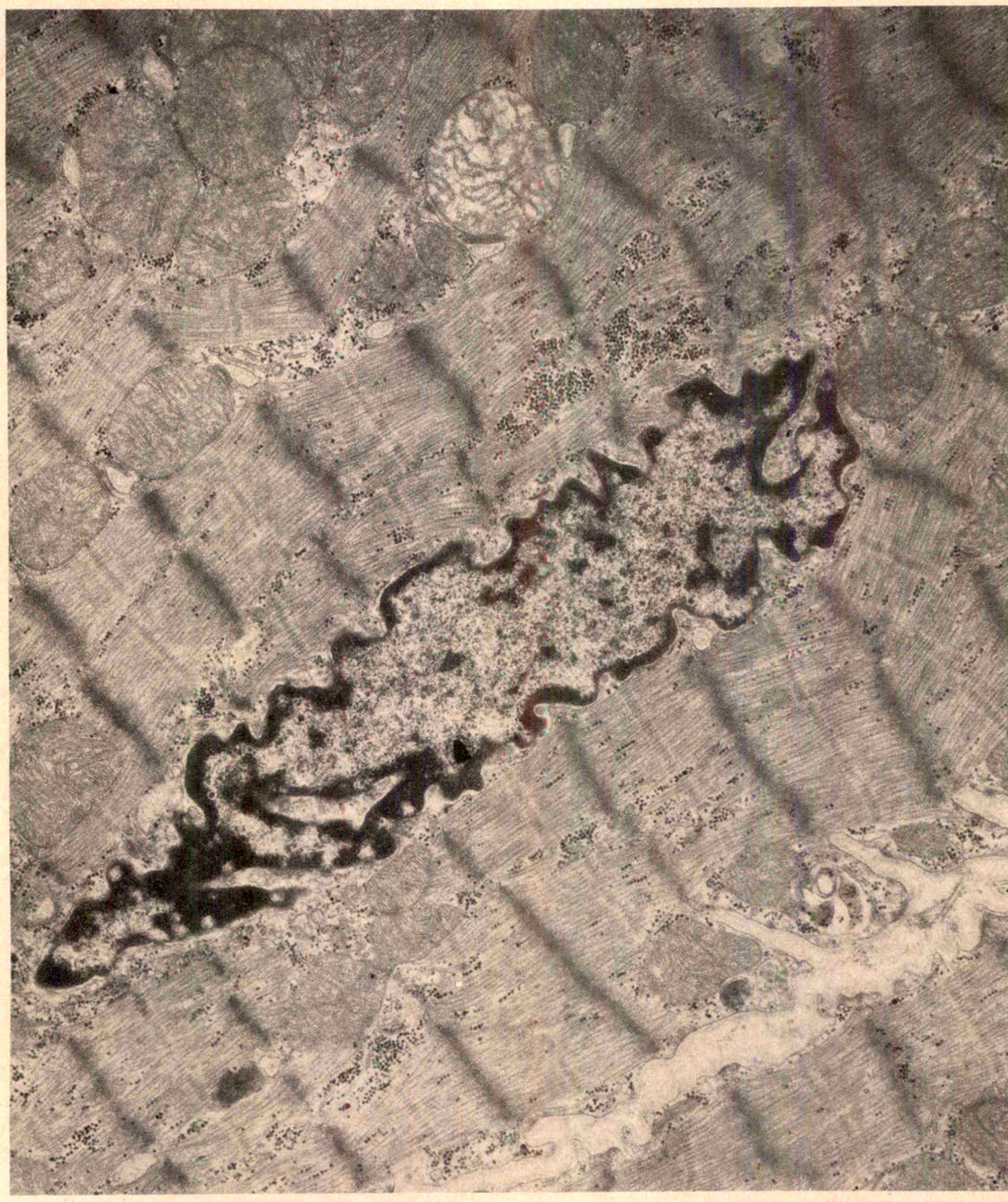

FIGURE 14. Photomicrograph showing nuclear morphologic features in the epicardial layer of the ischemic zone after 4 hours of coronary occlusion. In comparison with Figure 11, there is less margination and clumping of nuclear chromatin. Early ischemic changes are also evident from the slight swelling of the mitochondria and the relative decrease in glycogen. (×30,000, reduced by 22 percent.)

References

1. **Braunwald E, Maroko PR:** The reduction of infarct size. An idea whose time (for testing) has come. Circulation 50:206–209, 1974
2. **Maroko PR, Kjekshus JK, Sobel BE, et al:** Factors influencing infarct size following coronary artery occlusion. Circulation 43: 67–82, 1971
3. **Banka VS, Helfant RH:** Temporal sequence of dynamic contractile characteristics in ischemic and nonischemic myocardium after acute coronary ligation. Am J Cardiol 34:158–163, 1974
4. **Banka VS, Chadda KD, Helfant RH:** Limitations of myocardial revascularization in restoration of regional contraction abnormalities produced by coronary occlusion. Am J Cardiol 34:164–170, 1974
5. **Bodenheimer MM, Banka VS, Levites R, et al:** Temporal relation of epicardial electrographic, contractile and biochemical changes after acute coronary occlusion and reperfusion. Am J Cardiol 37:486–492, 1976
6. **Tyberg JV, Forrester JS, Wyatt HL, et al:** An analysis of segmental ischemic dysfunction utilizing the pressure-length loop. Circulation 49:748–754, 1974
7. **Vokonas PS, Pirzada FA, Hood WB:** Experimental myocardial infarction. XII. Dynamic changes in segmental mechanical behavior of infarcted and noninfarcted myocardium. Am J Cardiol 37: 853–859, 1976
8. **Shell WE, Sobel BE:** Biochemical markers of ischemic injury. Circulation 53:Suppl I:I-98–I-106, 1976
9. **Cox JL, Daniel TM, Boineau JP:** Electrophysiologic time-course of acute myocardial ischemia and the effects of early coronary artery reperfusion. Circulation 48:971–983, 1973
10. **Bodenheimer MM, Banka VS, Hermann GA, et al:** Reversible asynergy: histopathologic and electrographic correlations in patients with coronary artery disease. Circulation 53:792–796, 1976
11. **Bodenheimer MM, Banka VS, Trout RG, et al:** Local characteristics of the normal and asynergic left ventricle in man. Am J Med 61: 650–656, 1976
12. **Kloner RA, Ganote CE, Whalen DA, et al:** Effect of transient period of ischemia on myocardial cells. Am J Pathol 74:399–413, 1974
13. **Rivas F, Cobb FR, Bache RJ, et al:** Relationship between blood flow to ischemic regions and extent of myocardial infarction. Circ Res 38:439–447, 1976
14. **Jennings RB, Sommers HM, Smyth GA, et al:** Myocardial necrosis induced by temporary occlusion of a coronary artery in the dog. Arch Pathol 70:68–78, 1960
15. **Reimer KA, Rasmussen MM, Jennings RB:** Reduction by propranolol of myocardial necrosis following temporary coronary artery occlusion in dogs. Circ Res 38:353–363, 1973
16. **Reimer KA, Lowe JE, Rasmussen MM, et al:** The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. Circulation 56:786–794, 1977
17. **Banka VS, Bodenheimer MM, Helfant RH:** Nitroglycerin in experimental myocardial infarction. Am J Cardiol 36:453–458, 1975
18. **Banka VS, Bodenheimer MM, Helfant RH:** Effect of nitroprusside on local contractile performance after coronary ligation and reperfusion. Am J Cardiol 37:544–549, 1976

Computer-Assisted Reporting System for the Follow-Up of Patients With Prosthetic Heart Valves

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The implantation of large numbers of prosthetic heart valves carries with it the responsibility for continual reassessment of all aspects of patient management. Experience with more than 2,000 prosthetic valve operations since 1963 led to the development of a comprehensive computer-assisted data collection, management and reporting system. Over a 5 year period, data forms were developed for the detailed documentation of preoperative, intraoperative and postoperative information. These were designed in the form of checklists suitable for direct computer entry with use of mark-sense document readers. Special emphasis was placed on preoperative assessment of ventricular function, valve selection, intraoperative myocardial preservation, postoperative rehabilitation and prosthetic valve-related complications. This system makes possible rapid computer generation of a variety of reports to the referring physician regarding the individual patient and to the clinical investigator in relation to patient group statistics. Also, questionnaires to patients or physicians, or both, to update patient data can be produced by the computer at appropriate intervals after valve surgery. Experience indicated that a computer-assisted methodology is the only practical way to provide adequate follow-up of large groups of patients. Additionally, direct access to relevant information helps to create an environment in which essential research can be carried out in the face of a demanding clinical practice.

To study a large patient population in detail, one must have the means for both accumulating and retrieving a massive amount of clinical data. Our experience since 1963 with prosthetic valve operations in more than 2,000 patients has demonstrated that a computer-assisted reporting system is essential in meeting this requirement.

In 1970, a prosthetic valve follow-up clinic was established at the Toronto General Hospital to screen patients for the presence of ball variance. A follow-up form developed for this purpose included only the essential information relevant to the problem. It soon became evident that a great deal more information could be gleaned from our total patient population if a standardized reporting system were used, and several generations of follow-up forms were thus developed to achieve this purpose. Through this process, we were able to determine what information was relevant and to strike a balance between being so brief as to be incomplete and so detailed as to be impractical. Although we were successful in accumulating a vast quantity of patient information, we had difficulty in gaining access to these data because there was no practical system for the selective retrieval of information pertinent to a specific study. In 1973, we decided that future data should be collected in a format that would permit keypunch entry onto a computer and in 1974 we produced our first generation of such computer-compatible forms. To minimize the time commitment required for the manual

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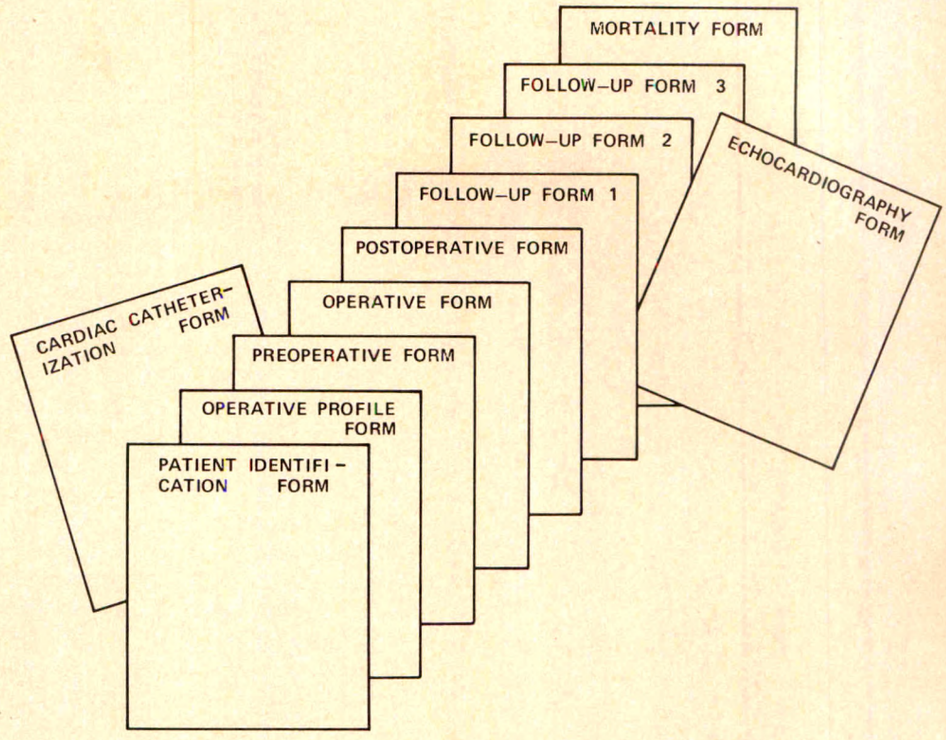

FIGURE 1. Organization of the basic forms of the computer-assisted reporting system. Supplementary forms can be added. As examples, the integration of a cardiac catheterization form with the preoperative assessment and an echocardiography form with a follow-up assessment are illustrated.

transfer of information onto the computer, the follow-up forms were subsequently printed in a format suitable for direct computer entry by mark-sense document readers.

The Computer-Assisted Reporting System

Our computer-assisted reporting system was designed to achieve three broad objectives: (1) to define clearly the indications for valve replacement and criteria for prosthetic valve selection, (2) to establish the intraoperative determinants of the outcome of prosthetic valve replacement, and (3) to monitor valve-related complications and to assess the functional and rehabilitation status of the patient in the postoperative period.

The basic forms for our computer-assisted reporting system are illustrated in Figure 1. The first two forms consist of a patient identification form and an operative profile form in keypunch format; the next five forms are in mark-sense format for the documentation of preoperative, operative, postoperative, follow-up and mortality data. The preoperative, operative and postoperative forms are used as many times as the individual patient undergoes valve-related operations. In contrast, the number of follow-up forms filled out is determined by the number of visits by the patient to the prosthetic valve follow-up clinic. In addition, supplementary forms may be integrated into the reporting system. These can include detailed hemodynamic and angiographic data obtained from cardiac catheterization, special studies

TABLE I

Operation Codes

01 Aortic valve replacement	20 Reconstruction of ascending aorta
02 Mitral valve replacement	21 ASD closure
03 Tricuspid valve replacement	22 VSD closure
04 Repair of aortic valve prosthesis	23 Permanent pacemaker
05 Repair of mitral valve prosthesis	24 Internal mammary implant, single
06 Repair of tricuspid valve prosthesis	25 Internal mammary implant, double
07 Exploration of aortic valve	26 Resection/plication of ventricular wall
08 Exploration of mitral valve	27 ACB, right coronary artery
09 Exploration of tricuspid valve	28 ACB, main left coronary artery
10 Aortic valvotomy, closed	29 ACB, left anterior descending coronary artery
11 Aortic valvotomy, open	30 ACB, left circumflex coronary artery
12 Mitral valvotomy, closed	31 Coronary, endarterectomy, right
13 Mitral valvotomy, open	32 Coronary, endarterectomy, left
14 Tricuspid valvotomy	33 Intraaortic balloon pump
15 Mitral anuloplasty	34 Emergency surgery in a moribund patient
16 Tricuspid anuloplasty	35 Urgent surgery in an unstable patient
17 Reconstruction of pulmonary outflow tract	36 Cardiac transplantation
18 Ventriculomyotomy	37 Implantation of ventricular assist device
19 Repair of ruptured sinus of Valsalva	38 Other (specify_____)

ACB = aortocoronary bypass surgery; ASD = atrial septal defect; VSD = ventricular septal defect.

such as echocardiography, phonocardiography and nuclear angiography as well as reports of exercise tests and general assessments of rehabilitation status.

Detailed Description

Patient identification form (Fig. 2): This form contains such basic data as the patient's name, address, telephone number, social insurance/security number, hospital identification/chart number, insurance number, date of birth, sex and names of referring physicians. A unique identification number is used for each patient. This consists of the patient's chart number at our institution. In addition, space is provided under the heading "office use only" to permit the identification of the patient as a member of a specific study group. Entries under "coded information" may be used for additional identifying data not included in the balance of the form. The data contained in the patient identification form are keypunched onto the computer and updated as necessary.

Operative profile form (Fig. 3): This form is a sequential record of all cardiac operative procedures for an individual patient. This form provides, at a glance, the complete cardiac operative history including prosthetic valve implantations identified with respect to date, surgeon, hospital, valve position, model and size, as well as repairs and replacements of any of the prostheses. Space is provided to document other cardiac procedures performed separately or in association with a prosthetic valve operation. These procedures are listed using a uniform code that we have adopted for all cardiac surgical patients (Table I). Entries under "additional coded infor-

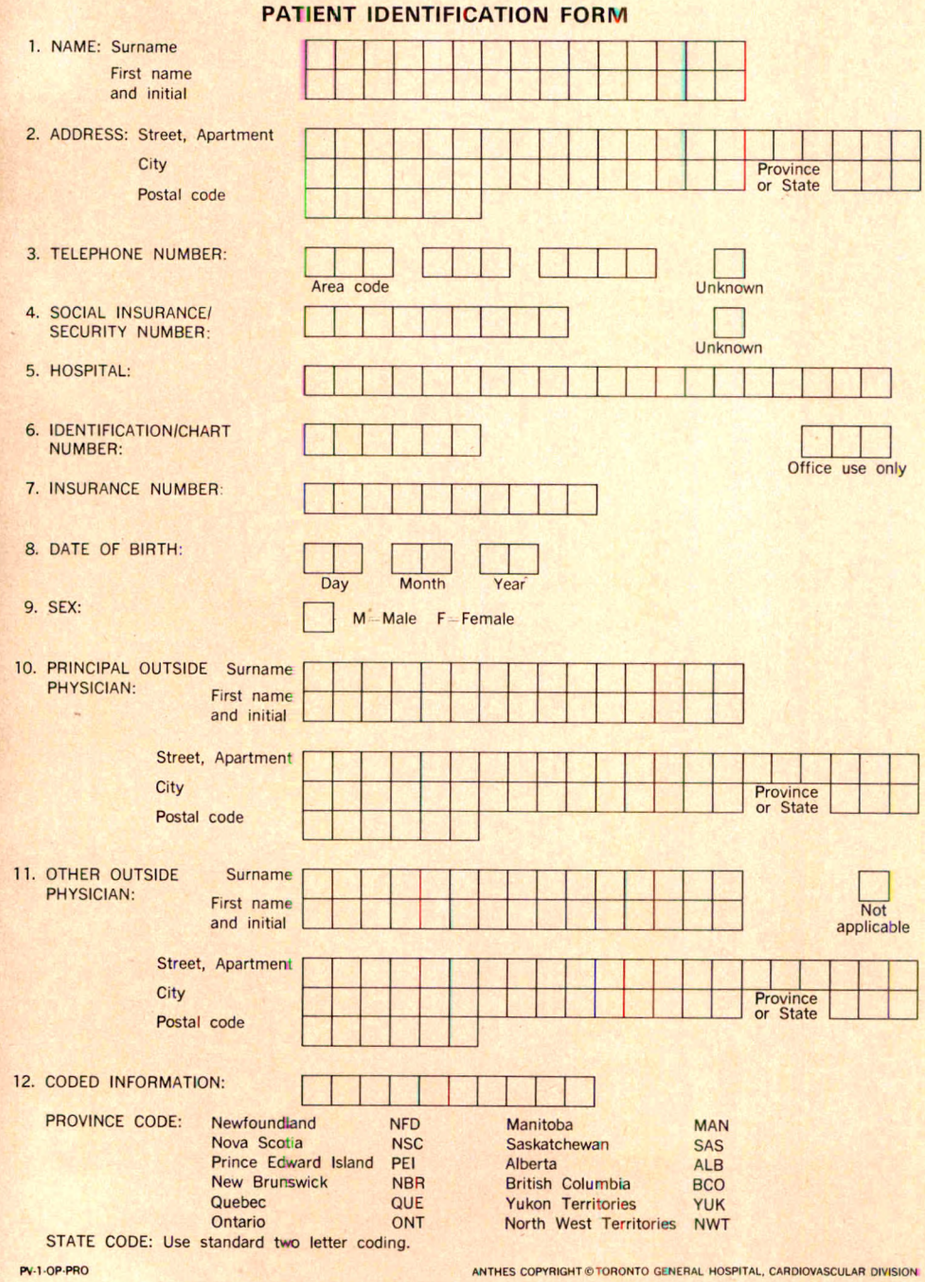

FIGURE 2. Patient identification form.

mation" may be used for any data not included in the balance of the form. The data contained in this form are also key-punched onto the computer and updated as necessary. The operative profile form is designed to allow for any possible combination and permutation of cardiac procedures with respect to either the same or separate operations, as shown by the worked example in Figure 3. The sequencing of all other forms in the reporting system relates to the dates of the various operative procedures so that the operative profile form becomes the pivotal organizing element in the system of forms.

Preoperative form (Fig. 4): This form and remaining basic forms in the reporting system have been designed as checklists suitable for direct computer entry by means of mark-sense document readers. The data are entered onto the form by the simple process of blackening the appropriate areas with an ordinary lead pencil. The mark-sense forms have 64 lines available for data entry and all begin with the patient identification/chart number. Space is also provided for the names of the patient and the physician completing the form and other related data. This information is helpful in the day to day use of the forms and, because the physician completing the form is identified, responsibility for the completeness and accuracy of the data obtained can be assigned.

The preoperative form includes the date of the associated cardiac catheterization, the report of which may be added as a supplementary form (Fig. 1). The balance of the form includes a detailed functional enquiry under the headings of New York Heart Association functional class; symptoms; history of thromboembolism or endocarditis, or both; employment status; and medications. Space is provided for recording information on the electrocardiogram, including estimation of Estes left ventricular hypertrophy point score, special studies, hemoglobin, reticulocyte count, lactate dehydrogenase and cardiothoracic ratio. Reports of special studies, including echocardiography, phonocardiography, exercise test and nuclear angiography, may also be added as supplementary forms. The preoperative form concludes with the date of the associated operation.

Operative form (Fig. 5): This form pertains only to prosthetic valve operations and includes the date of operation and direct observations by the surgeon of gross valve disease or coronary artery, ventricular, atrial or other significant disease. Technical details with regard to cardiopulmonary bypass, myocardial protection, suture techniques and intraoperative complications are also recorded.

Postoperative form (Fig. 6): This form describes the patient's postoperative course in the hospital with special emphasis on prosthetic valve-related complications, infection, postoperative length of hospital stay and medications on discharge. These observations provide a basis for comparison in subsequent follow-up assessments. If more than one prosthetic valve-related operation is performed during the same hospital admission, preoperative and postoperative forms are filled out for each operation but the postoperative length of stay is calculated from the date of the last operation.

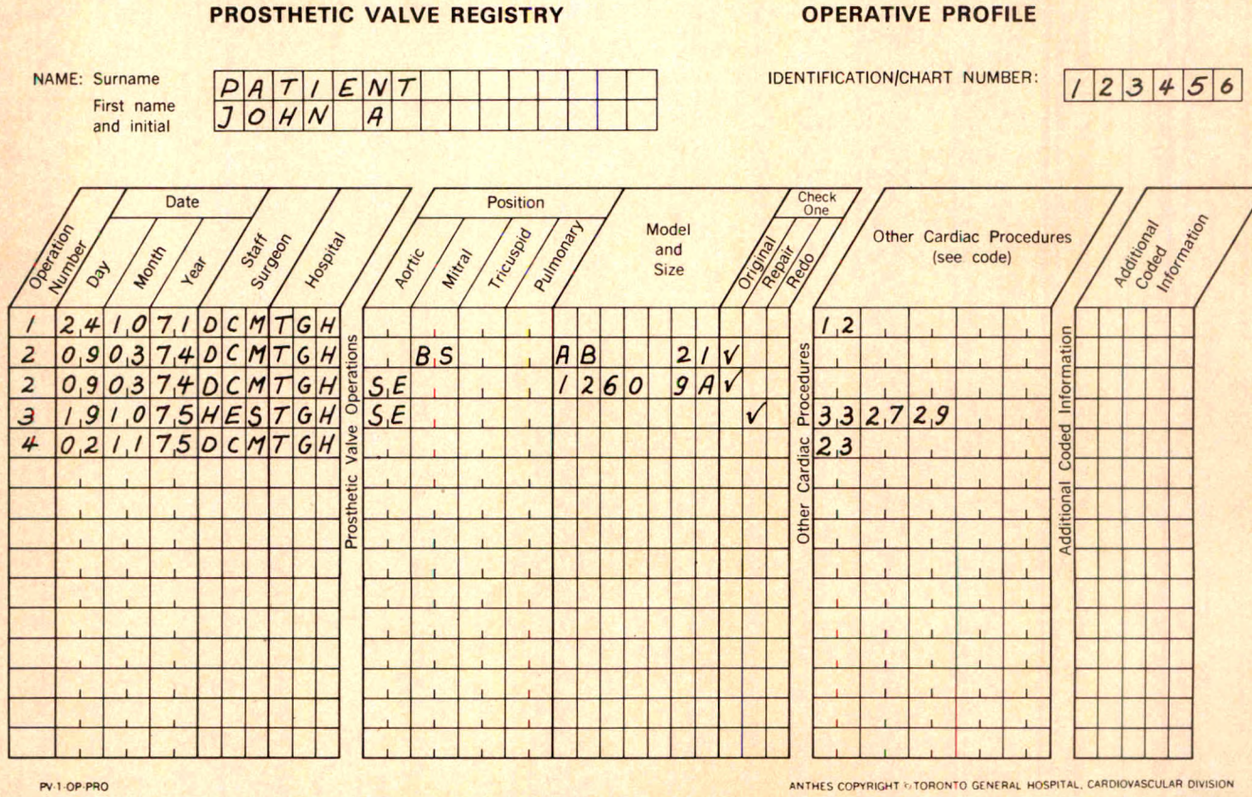

FIGURE 3. Operative profile form completed for a hypothetical case. This patient had a closed mitral valvotomy (12) in 1971 followed by replacement of the aortic and mitral valves in 1974 using Starr-Edwards (SE) and Bjork-Shiley (BS) prostheses, respectively. In 1975, the Starr-Edwards aortic prosthesis was repaired, and at this time vein grafting to the right (27) and left anterior descending (29) coronary arteries was performed with the aid of an intraaortic balloon pump (33). This procedure was complicated by complete heart block, and a permanent pacemaker (23) was implanted 2 weeks later.

PROSTHETIC VALVE REGISTRY — PREOPERATIVE FORM

PATIENT IDENTIFICATION
IDENTIFICATION / CHART NUMBER: _____
SURNAME: _____
FIRST NAME AND INITIAL: _____
ATTENDING CARDIOLOGIST: _____
PHYSICIAN COMPLETING FORM: _____
HOSPITAL OF CATHETERIZATION: _____

ASSOCIATED CARDIAC CATHETERIZATION:
Day: 1 2 3 4 5 6 7 8 9 0 X UNK
Month: 1 2 3 4 5 6 7 8 9 0 X UNK
Year: 1 2 3 4 5 6 7 8 9 0 X UNK

NYHA FUNCTIONAL CLASS: See code — 1 2a 2b 3 4 X UNK
SYMPTOMS: A=None B=Angina C=Fatigue D=SOB E=Orthopnea F=PND G=Palpitations H=Syncope I=SOA — Limiting (one): A B C D E F G H I X UNK; Other: A B C D E F G H I X UNK
HISTORY OF THROMBOEMBOLISM: Y=Yes N=No — Y N X UNK
If yes, A=Cerebral B=Peripheral — Total number (1-8): A B 1 2 3 4 5 6 7 8 X UNK
ENDOCARDITIS: Y=Yes N=No — Y N X UNK
If yes, A=Active B=Treated within past three months C=Remote — A B C X UNK
EMPLOYMENT STATUS: A=Full time B=Part time C=Unemployed D=Housework — A B C D X UNK
If "B" or "D", percentage of time: 1 2 3 4 5 6 7 8 9 0 X UNK
If not working, A=Physically unable B=Emotionally unable C=Physician's advice D=Retirement age E=Employer will not hire F=Not motivated — A B C D E F X UNK
MEDICATIONS: A=None B=Digitalis C=Diuretics D=Potassium E=Inderal F=Quinidine G=Pronestyl H=Anticoagulants I=Antiplatelet agents J=Nitrates — A B C D E F G H I J X UNK
ELECTROCARDIOGRAM: A=NSR B=Atrial fibrillation C=Atrial flutter D=Pacer E=Other — A B C D E X UNK
Estes LVH point score — See code: 1 2 3 4 5 6 7 8 9 0 X UNK
LV strain — Y=Yes N=No: Y N X UNK
Infarction — A=None B=Ant C=Inf D=Lat E=Post: A B C D E X UNK
SPECIAL STUDIES: A=Echo 1D B=Echo 2D C=Phono D=Exercise test E=Nuclear angio — A B C D E X UNK
HEMOGLOBLIN: (g/100ml): 1 2 3 4 5 6 7 8 9 0 X UNK; .1 .2 .3 .4 .5 .6 .7 .8 .9 .0 X UNK
RETICULOCYTE COUNT: (%): 1 2 3 4 5 6 7 8 9 0 X UNK; .1 .2 .3 .4 .5 .6 .7 .8 .9 .0 X UNK
LDH: (IU): 1 2 3 4 5 6 7 8 9 0 X UNK
CARDIOTHORACIC RATIO: Calculate % — ___ ___.___/___ ___.___ cm: 1 2 3 4 5 6 7 8 9 0 X UNK

DATE OF OPERATION:
Day: 1 2 3 4 5 6 7 8 9 0 X UNK
Month: 1 2 3 4 5 6 7 8 9 0 X UNK
Year: 1 2 3 4 5 6 7 8 9 0 X UNK

FORM NO. 50919 PV-1-PREOP

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FIGURE 4. Preoperative form.

PROSTHETIC VALVE REGISTRY — OPERATIVE FORM

PATIENT IDENTIFICATION

IDENTIFICATION / CHART NUMBER: _____

SURNAME: _____

FIRST NAME AND INITIAL: _____

SURGEON: _____

PHYSICIAN COMPLETING FORM: _____

DATE OF OPERATION:

Day: 1 2 3 4 5 6 7 8 9 0 — X UNK

Month: 1 2 3 4 5 6 7 8 9 0 — X UNK

Year: 1 2 3 4 5 6 7 8 9 0 — X UNK

GROSS VALVE PATHOLOGY: S=Stenotic I=Insufficient E=Endocarditis N=Normal NA=Not assessed Calcium (0-4+)

Aortic: S I E N NA 0+ 1+ 2+ 3+ 4+ — X UNK

Mitral: S I E N NA 0+ 1+ 2+ 3+ 4+ — X UNK

Tricuspid: S I E N NA 0+ 1+ 2+ 3+ 4+ — X UNK

Pulmonary: S I E N NA 0+ 1+ 2+ 3+ 4+ — X UNK

GROSS CORONARY ARTERY PATHOLOGY: Y=Yes N=No NA=Not assessed

RCA: Y N NA — LAD: Y N NA — X UNK

LCA: Y N NA — CIRC: Y N NA — X UNK

GROSS LEFT VENTRICULAR PATHOLOGY: A=Hypertrophy B=Dilatation C=Fibrosis D=Aneurysm E=Normal NA=Not assessed

A B C D E NA — X UNK

GROSS ATRIAL PATHOLOGY: A=Dilated B=Friable C=Thrombus D=Normal NA=Not assessed

RA: A B C D NA — X UNK

LA: A B C D NA — X UNK

OTHER SIGNIFICANT PATHOLOGY: Y=Yes N=No

Y N — X UNK

HEMODILUTION: Y=Yes N=No

Y N — X UNK

HYPOTHERMIA: A=Mild (33° - 37°) B=Moderate (28° - 32°) C=Intermediate (20° - 27°) D=Deep (<20°) E=Core F=Local G=Both

A B C D E F G — X UNK

CHEMICAL CARDIOPLEGIA: Y=Yes N=No

Y N — X UNK

LEFT HEART VENT: Y=Yes N=No

Y N — X UNK

If yes, A=Ventricular B=Atrial C=Other

A B C — X UNK

DURATION OF BYPASS: (min)

1 2 3 4 5 6 7 8 9 0 — X UNK

1 2 3 4 5 6 7 8 9 0 — X UNK

1 2 3 4 5 6 7 8 9 0 — X UNK

DURATION OF CLAMPING: (min)

1 2 3 4 5 6 7 8 9 0 — X UNK

1 2 3 4 5 6 7 8 9 0 — X UNK

1 2 3 4 5 6 7 8 9 0 — X UNK

DURATION OF CORONARY ISCHEMIA: (min)

Right: 1 2 3 4 5 6 7 8 9 0 — X UNK

1 2 3 4 5 6 7 8 9 0 — X UNK

1 2 3 4 5 6 7 8 9 0 — X UNK

Left: 1 2 3 4 5 6 7 8 9 0 — X UNK

1 2 3 4 5 6 7 8 9 0 — X UNK

1 2 3 4 5 6 7 8 9 0 — X UNK

CORONARY PERFUSION: A=Continuous B=Intermittent C=None

Right: A B C — X UNK

Left: A B C — X UNK

CORONARY CANNULAE: A=Ring B=Balloon C=Other D=Large E=Medium F=Small G=None

Right: A B C D E F G — X UNK

Left: A B C D E F G — X UNK

VENTRICULAR FIBRILLATION: A=Induced B=Spontaneous C=Both D=Intermittent E=Continuous F=Countershock required G=None

A B C D E F G — X UNK

EMPTY BEATING HEART: A=Intermittent B=Continuous C=None

A B C — X UNK

COUNTERPULSATION REQUIRED: A=Preoperative B=Operative C=Postoperative D=None

A B C D — X UNK

SUTURE TECHNIQUE: A=Interrupted B=Continuous C=Pledgets

Aortic: A B C — Tricuspid: A B C — X UNK

Mitral: A B C — Pulmonary: A B C — X UNK

SIGNIFICANT HEART BLOCK: Y=Yes N=No

Y N — X UNK

SUPPORT DRUGS REQUIRED: A=Isoproterenol B=Dopamine C=Digitalis D=Catecholamines E=Other F=None

A B C D E F — X UNK

PERFUSION PROBLEMS: Y=Yes N=No

Y N — X UNK

ANESTHESIA PROBLEMS: Y=Yes N=No

Y N — X UNK

TECHNICAL PROBLEMS: Y=Yes N=No

Y N — X UNK

BLEEDING PROBLEMS: Y=Yes N=No R=Reoperation for bleeding

Y N R — X UNK

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FIGURE 5. Operative form.

Follow-up form (Fig. 7): This form is not linked to any particular operative procedure but is used after the first prosthetic valve operation to record assessments after hospital discharge. It includes essentially the same questions that appear on both the preoperative and postoperative forms. Follow-up visits may be scheduled for a variety of reasons, including a routine annual assessment, a change in symptoms or functional status, development of a valve-related complication, a research follow-up on a specific patient group or special circumstances such as a prosthetic valve recall or a preoperative assessment for a noncardiac operation.

Mortality form (Fig. 8): Finally, the mortality form indicates the date of death and includes the clinically ascertained cause of death as well as the autopsy findings when available. Provision has also been made for a description of the presence and severity of structural alterations in the explanted prostheses.

Discussion

The implementation of a computer-assisted reporting system such as we have described involves the cooperation of a large team that includes surgeons, cardiologists, pathologists, research assistants and computer personnel. Success depends most critically on rigid control over the accuracy and completeness of all data collected and, we believe, demands the appointment of a "quality control officer." In our experience, such a person is required to ensure that the forms are actually filled out appropriately and to remind the physician involved to remedy specific cases of inaccurate or incomplete responses to questions on the forms. An additional safeguard has been built into our reporting system in that the computer rejects any form in which an incomplete or inappropriate response appears. If data to answer a specific question are unknown, the physician fills in the far right column labeled UNK, whereas if the question is not applicable the response is designated X. This procedure ensures that those filling out the form provide a response for every question.

Our computer-assisted reporting system is capable of fulfilling a number of important service functions. These include the generation of a supplemental oper-

PROSTHETIC VALVE REGISTRY — POSTOPERATIVE FORM

PATIENT IDENTIFICATION
IDENTIFICATION/ CHART NUMBER: _____
SURNAME: _____
FIRST NAME AND INITIAL: _____
ATTENDING CARDIOLOGIST: _____
PHYSICIAN COMPLETING FORM: _____
DATE OF OPERATION: Day / Month / Year

HISTORY OF THROMBOEMBOLISM: Y=Yes N=No — Y N — X UNK
If yes, A=Cerebral B=Peripheral Total number (1-8) — A B 1 2 3 4 5 6 7 8 — X UNK
Postoperative month of first embolus — 1 2 3 4 5 6 7 8 9 0 — X UNK

PROSTHETIC VALVE ENDOCARDITIS: Y=Yes N=No P=Possible — Y N P — X UNK

INSUFFICIENCY MURMUR OF PROSTHESIS: Aortic / Mitral / Tricuspid — 0+ 1+ 2+ 3+ 4+ 5+ 6+ NA Y N — X UNK
Grade (0-6+) NA=Not assessed
Varying intensity Y=Yes N=No

DIASTOLIC MURMUR OF MITRAL PROSTHESIS: — 0+ 1+ 2+ 3+ 4+ 5+ 6+ NA — X UNK
Grade (0-6+) NA=Not assessed

OPENING SOUNDS: A=Normal B=Abnormal NA=Not assessed — Aortic: A B NA; Mitral: A B NA — X UNK
CLOSING SOUNDS: A=Normal B=Abnormal NA=Not assessed — Aortic: A B NA; Mitral: A B NA — X UNK

WOUND INFECTION: Y=Yes N=No — Y N — X UNK
STERNAL DEHISCENCE: Y=Yes N=No — Y N — X UNK
REACTIVATION SYNDROME: Y=Yes N=No P=Possible — Y N P — X UNK

POSTOPERATIVE LENGTH OF STAY: Days — 1 2 3 4 5 6 7 8 9 0 — X UNK

DISCHARGE MEDICATIONS: A=None B=Digitalis C=Diuretics D=Potassium E=Inderal F=Quinidine G=Pronestyl H=Anticoagulants I=Antiplatelet agents J=Nitrates — A B C D E F G H I J — X UNK

FORM NO. 50919 PV-1-POSTOP

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FIGURE 6. Postoperative form.

PROSTHETIC VALVE REGISTRY — FOLLOW-UP FORM

PATIENT IDENTIFICATION

IDENTIFICATION / CHART NUMBER: _____

SURNAME: _____
FIRST NAME AND INITIAL: _____
PHYSICIAN COMPLETING FORM: _____

DATE OF FOLLOW UP:
- Day: 1 2 3 4 5 6 7 8 9 0 | X UNK
- Month: 1 2 3 4 5 6 7 8 9 0 | X UNK
- Year: 1 2 3 4 5 6 7 8 9 0 | X UNK

NYHA FUNCTIONAL CLASS: See code — 1 2a 2b 3 4 | X UNK

SYMPTOMS: A=None B=Angina C=Fatigue D=SOB E=Orthopnea F=PND G=Palpitations H=Syncope I=SOA
- Limiting (one): A B C D E F G H I | X UNK
- Other: A B C D E F G H I | X UNK

SUBJECTIVE RESPONSE TO SURGERY: A=Greatly improved B=Moderately improved C=Slightly improved D=Same E=Worse — A B C D E | X UNK

EMPLOYMENT STATUS: A=Full time B=Part time C=Unemployed D=Housework — A B C D | X UNK
- If "B" or "D", percentage of time: 1 2 3 4 5 6 7 8 9 0 | X UNK
- If not working, A=Physically unable B=Emotionally unable C=Physician's advice D=Retirement age E=Employer will not hire F=Not motivated — A B C D E F | X UNK

MEDICATIONS: A=None B=Digitalis C=Diuretics D=Potassium E=Inderal F=Quinidine G=Pronestyl H=Anticoagulants I=Antiplatelet agents J=Nitrates — A B C D E F G H I J | X UNK

HISTORY OF THROMBOEMBOLISM: Y=Yes N=No — Y N | X UNK
- If yes, A=Cerebral B=Peripheral — A B | X UNK
- Total number (1-8) — 1 2 3 4 5 6 7 8 | X UNK
- Postoperative month of first embolus: 1 2 3 4 5 6 7 8 9 0 | X UNK

SIGNIFICANT ANTICOAGULANT HEMORRHAGE: Y=Yes N=No P=Possible — Y N P | X UNK
- Number since surgery — 1 2 3 4 5 6 7 | X UNK

PROSTHETIC VALVE ENDOCARDITIS SINCE SURGERY: Y=Yes N=No P=Possible — Y N P | X UNK

INSUFFICIENCY MURMUR OF PROSTHESIS: Grade (0-6+) NA=Not assessed Varying intensity Y=Yes N=No
- Aortic: 0+ 1+ 2+ 3+ 4+ 5+ 6+ NA Y N | X UNK
- Mitral: 0+ 1+ 2+ 3+ 4+ 5+ 6+ NA Y N | X UNK
- Tricuspid: 0+ 1+ 2+ 3+ 4+ 5+ 6+ NA Y N | X UNK

DIASTOLIC MURMUR OF MITRAL PROSTHESIS: Grade (0-6+) NA=Not assessed — 0+ 1+ 2+ 3+ 4+ 5+ 6+ NA | X UNK

OPENING SOUNDS: A=Normal B=Abnormal NA=Not assessed
- Aortic: A B NA | X UNK
- Mitral: A B NA | X UNK

CLOSING SOUNDS: A=Normal B=Abnormal NA=Not assessed
- Aortic: A B NA | X UNK
- Mitral: A B NA | X UNK

ELECTROCARDIOGRAM: A=NSR B=Atrial fibrillation C=Atrial flutter D=Pacer E=Other — A B C D E | X UNK
- Estes LVH point score See code: 1 2 3 4 5 6 7 8 9 0 | X UNK
- LV strain Y=Yes N=No: Y N | X UNK
- Infarction A=None B=Ant C=Inf D=Lat E=Post: A B C D E | X UNK

SPECIAL STUDIES: A=Echo 1D B=Echo 2D C=Phono D=Exercise test E=Nuclear angio — A B C D E | X UNK

HEMOGLOBIN: (g/100 ml): 1 2 3 4 5 6 7 8 9 0 | X UNK; 1 2 3 4 5 6 7 8 9 0 | X UNK; .1 .2 .3 .4 .5 .6 .7 .8 .9 .0 | X UNK

RETICULOCYTE COUNT: (%): 1 2 3 4 5 6 7 8 9 0 | X UNK; 1 2 3 4 5 6 7 8 9 0 | X UNK; .1 .2 .3 .4 .5 .6 .7 .8 .9 .0 | X UNK

LDH: (IU): 1 2 3 4 5 6 7 8 9 0 | X UNK; 1 2 3 4 5 6 7 8 9 0 | X UNK; 1 2 3 4 5 6 7 8 9 0 | X UNK

CARDIOTHORACIC RATIO: Calculate %
__ __ . __ / __ __ . __ cm — 1 2 3 4 5 6 7 8 9 0 | X UNK

FORM NO. 50919 PV-1-FU

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FIGURE 7. Follow-up form.

ative report for the patient's record, follow-up reports to the referring physician, notification of clinic appointments to the patient and questionnaires to the patient and referring physician. The system can also be used to facilitate a wide variety of clinical research studies. Examples of research questions that are currently of interest to us are: To what extent does a high pulmonary vascular resistance alter operative mortality and late results in mitral valve replacement? How does ischemic arrest compare with chemical cardioplegia in relation to long-term left ventricular function in aortic valve replacement? How do various models of heart valve prostheses perform in terms of durability, hemodynamic efficiency and biocompatibility? These are just a few examples.

In conclusion, we submit that a computer-assisted methodology is the only practical way to provide adequate follow-up on a large population of patients. Additionally, direct access to relevant information helps to create an environment in which essential research can be carried out in the face of a demanding clinical practice.

PROSTHETIC VALVE REGISTRY — MORTALITY FORM

PATIENT IDENTIFICATION
IDENTIFICATION / CHART NUMBER: _____
SURNAME: _____
FIRST NAME AND INITIAL: _____
PHYSICIAN COMPLETING FORM: _____

TIME OF DEATH: A=Operative B=Early (within 30 days) C=Late

DATE OF DEATH: Day / Month / Year

CLINICAL CAUSE OF DEATH:
A=Thrombosis/Embolism B=Infection C=Dehiscence
D=Hemorrhage E=Ball Variance
F=Myocardial infarction G=Myocardial failure
H=Cardiac (other) I=Non cardiac
J=Sudden death (unexplained) K=Not yet determined

AUTOPSY PERFORMED: Y=Yes N=No

AUTOPSY NUMBER:

AUTOPSY RESTRICTED TO HEART: Y=Yes N=No

AUTOPSY CAUSE OF DEATH:
A=Thrombosis/Embolism B=Infection C=Dehiscence
D=Hemorrhage E=Ball variance
F=Myocardial infarction G=Myocardial failure
H=Cardiac (other) I=Non cardiac
J=Sudden death (unexplained) K=Not determined

STRUCTURAL ALTERATIONS IN EXPLANTED PROSTHESIS:
A=None B=Mild C=Moderate D=Severe

Structural changes in poppet or cusp	Aortic	A B C D
	Mitral	A B C D
	Tricuspid	A B C D
	Pulmonary	A B C D
Structural changes in struts or stent	Aortic	A B C D
	Mitral	A B C D
	Tricuspid	A B C D
	Pulmonary	A B C D
Structural changes in valve seat	Aortic	A B C D
	Mitral	A B C D
	Tricuspid	A B C D
	Pulmonary	A B C D

FORM NO. 50919 PV-1-MORT

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FIGURE 8. Mortality form.

Transvascular Endomyocardial Biopsy in Infants and Small Children: Description of a New Technique

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A miniaturized technique for transcatheter endomyocardial biopsy has been developed in the belief that myocardial biopsy performed in infancy, when the disease process in cardiomyopathy may be most active, should yield important etiologic and nosologic information. To obtain six biopsy specimens, three from each ventricle, adds about 1 hour to a diagnostic right and left heart catheterization. A no. 4 or 5 French forceps with a modified soft shaft is guided to the site in the apical septum of the right and left ventricles through a previously molded to measure guide tube of ultrathin radiopaque Teflon. With biplane fluoroscopy the guide tube is introduced as a sheath over a matching catheter and the catheter is removed. Contrast medium is injected to verify position, the forceps is introduced and the biopsy specimen is taken. If the forceps is sharp and pressure on the endocardium is light, evidence of biopsy is not discernible on examination of the heart 1 week later. The method was developed in small dogs and proved safe and effective in rabbits weighing 3 kg. Biopsy has been performed safely in children aged 4 1/2 months to 5 1/2 years and weighing 4.5 to 19.6 kg.

The understanding of diseases of cardiac muscle should be advanced by knowledge gained from greater use of myocardial biopsy. A biopsy technique for use in infants and children was devised to evaluate cardiomyopathy clinically manifest in these age groups, at a time when the disease process is early and active. This communication describes the biopsy technique and its use in 10 patients. Separate communications will deal with pathologic and virologic findings in the myocardium and the endocardium.

Material and Methods

Material and Equipment

The usual material described elsewhere[1] for percutaneous heart catheterization is used. Three additional items are necessary for the biopsy procedure: biopsy forceps, an ultrasonic cleaner bath and "molded to measure" catheter-guide tube sets that replace the diagnostic catheters. These items require ethylene oxide sterilization and a detoxification period of at least 1 day.

Each catheter-guide tube set consists of a forming stylet, an inner Teflon® catheter (no. 4 or 5 French) that is replaced by the biopsy forceps and an outer guide tube of ultrathin 4F or 5F radiopaque Teflon sheath tubing. An outline of the child's heart is traced from the posteroanterior and lateral roentgenograms. The position of the tricuspid and aortic valves and the size of the right and left ventricles and the aortic arch are estimated from these patterns as reconstructed conjecturally in three dimensions. Because these patterns are merely estimates, subject to later verification as the right and left ventriculograms are made during the catheterization, two guide tube sets of slightly different size are constructed for each ventricle. The one that appears to have the better fit is selected after ventriculography; the other is kept for standby use. First the stylets, of straight 0.023 inch (0.058 cm) mandrel wire (Cook, Inc., Bloomington, Indiana), are bent

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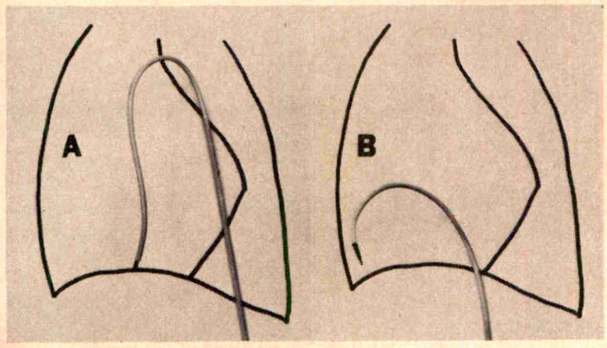

FIGURE 1. Patient 6. Tracings from a lateral roentgenogram to show the shape of the catheter-guide tube sets for the left ventricle **(A)** and right ventricle **(B).**

smoothly by hand into the desired curves. Stylets for the right ventricle are fashioned to curve as gently as possible from the inferior vena cava through the tricuspid valve toward the apex of the right ventricle, with a second short curve pointing the tip 90° posteriorly toward the septum. The stylets for the left ventricle are curved to pass as gently as possible around the aortic valve and down to the apex with a short second curve directed 90° anteriorly toward the septum (Fig. 1 and 2C). A radiopaque Teflon catheter (Cook, Inc.) (the inner catheter) is tapered distally to a single 0.025 inch (0.635 cm) hole and proximally is left without a hub. It is passed over the stylet so that the two distal ends match. The piece of radiopaque ultrathin Teflon sheath material (Universal Medical Instruments Corp., Ballston Spa, New York) that will become the guide tube is cut off sharply at both ends (supported by a bit of catheter inside it to prevent flattening) a few centimeters shorter than the inner catheter. The proximal end is flared, and an on-off stopcock with its lumen drilled large enough to accept the 5F biopsy forceps is attached. The distal end is advanced over the inner catheter to the beginning of its taper (Fig. 2A).

The lengths of the three components of each set are determined by the size of the patient. The guide tube should be about 5 cm longer than the distance from the groin to the biopsy site (Fig. 2C). The inner catheter is about 5 cm longer than the guide tube and the curved stylet is still longer by another 5 cm (Fig. 2B).

The four sets are assembled and their curved ends are immersed in boiling nonpyrogenic water for 15 minutes, then allowed to cool to room temperature, packed for protection against crushing and sterilized with ethylene oxide.

The no. 5F biopsy forceps used in larger patients is either the standard FB1C forceps supplied by Olympus Corporation of America, New Hyde Park, New York for use with their fiberoptic bronchoscope or a softer custom-made modification. For smaller patients a no. 4F bronchial biopsy forceps (Machida BF 1410) has been modified by substitution of an especially soft shaft (Machida America, Norwood, New Jersey) (Fig. 3). These forceps are all treated similarly. Before each use, the cutting edges are honed by hand under loupe magnification with a pencil-pointed Arkansas stone. The forceps is cleaned ultrasonically, rinsed in distilled water, dried in a stream of air, sprayed lightly with Teflon aerosol lubricant and subjected to sterilization with ethylene oxide. (Autoclaving damages the forceps.)

The gas-sterilized ultrasonic cleaner bath is placed on the operator's table and filled with heparinized saline solution for cleaning the biopsy forceps.

Biplane fluoroscopy adds greatly to the precise control of the biopsy procedure.

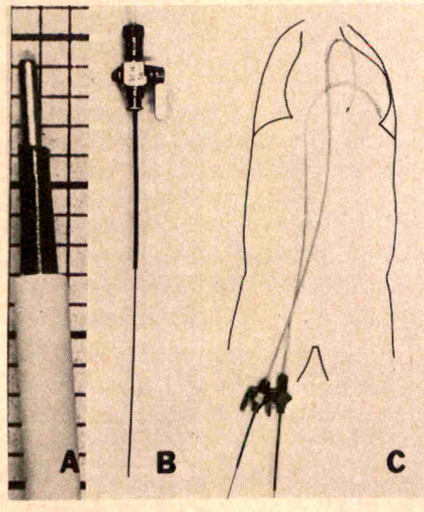

FIGURE 2. Patient 6. Details of the catheter-guide tube sets. **A,** the distal end of the set enlarged against a background of 1 mm squares, showing the innermost forming stylet of 0.023-inch mandrel wire, black Teflon no. 4F catheter tapered to the stylet and the outer guide tube of white radiopaque Teflon no. 4F sheath material. **B,** the proximal end of the set, showing the guide tube with the on-off stopcock, the inner catheter with no fitting (about 5 cm longer than the guide tube) and the stylet (about 5 cm longer than inner catheter); **C,** tracing of posteroanterior chest roentgenogram with an approximate sketch of trunk and thighs to illustrate the size and shape of the catheter-guide tube sets relative to this 4 1/2 kg patient. Each set has a double curve, that for the right ventricle finally curving 90° backward against the septum and that for the left ventricle finally curving 90° forward against the septum.

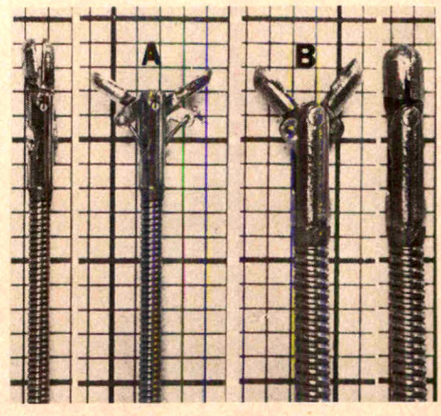

FIGURE 3. Details of the biopsy forceps in open and closed positions enlarged against a background of 1 mm squares: **A,** no. 4F (Machida BF 1410); **B,** no. 5F (Olympus FB-1C).

TABLE I

Biopsy Procedure in 10 Patients

Case no.	Age (yr)	Weight (kg)	C/T	Specimens/Attempts* RV	Specimens/Attempts* LV	Biopsy Time† (min)	TF Time‡ (min)
1	2.5	11.3	0.7	2/2	2/2	50	15
2	10 mo.	8.8	0.7	2/2	2/2	45	24
3*§	4	16.8	0.7	3/3	2/6	61	21
4§	3	12.6	0.5	0/0	1/1	10	15
5	2	9.8	0.8	3/3	3/3	50	26
6	4.5 mo.	4.5	0.8	3/3	1/1	37	20
7	7 mo.	7.5	0.7	2/2	3/3	32	15
8	1.5	5.9	0.8	3/3	2/6	122	20
9	5.5	19.6	0.6	3/3	3/3	56	32
10§	5	18.4	0.6	3/3	0/0	45	58

* Attempts = actual passages of forceps into ventricle.
† Time elapsed from end of diagnostic catheterization to end of biopsy procedure.
‡ Total fluoroscopic "on" time for diagnostic catheterization plus biopsy.
§ Case 3: Left ventricular biopsy could not be obtained in four attempts because of tough endocardium; two specimens contained endocardium only. Case 4: Elected to take only one specimen (patient's condition had improved). Case 10: Left ventricle could not be entered because of pseudocoarctation and aortic valve stenosis.
CT = cardiothoracic ratio by X-ray; LV = left ventricle; RV = right ventricle.

Technique of Biopsy

The patient is placed on the catheterization table in the usual manner, and the right and left sides of the heart are catheterized by way of the femoral artery and vein percutaneously using methods described previously.[1] After completion of the hemodynamic and cineangiographic studies, including biplane right and left ventriculography, the diagnostic catheter is removed from the femoral vein over a straight 0.021 or 0.025 inch (0.053 or 0.0635 cm) guide wire and is replaced by the selected guide tube-catheter pair after its stylet has been removed. With use of appropriate soft-tipped guide wire (straight or curved, or both) in advance for safe manipulation, the pair is gently advanced to a position in the right ventricle near the apical portion of the septum, a relatively safe and informative site for biopsy. Once there, the inner catheter is removed, the guide tube remaining in contact with the endocardium. Because it has only an end hole and a large bore, the guide tube must be retracted slightly to enable ventricular blood to fill it and displace all air. To prevent clots the guide tube is periodically aspirated and flushed with dilute heparin solution throughout the procedure. Total body heparinization is not needed.

The following steps are performed under fluoroscopic control: A small amount of dilute contrast medium is gently injected through the guide tube to enable visualization of the detail of the endocardial region undergoing biopsy. If the position needs much readjustment, it may be necessary to replace the inner catheter, reposition the pair, remove the inner catheter, flush and again inject contrast medium. When the desired position is verified, the biopsy forceps is advanced until it presents at the end of the guide tube. The guide tube is retracted 1 cm while the position of the forceps is maintained. This procedure uncovers the jaws, which are opened, advanced smoothly with only gentle pressure against the endocardium and then closed. While the jaws are held closed, the guide tube is advanced slightly and held in contact with the endocardium and the forceps is smoothly withdrawn from the tube. The sample is removed from the forceps and prepared for study. The forceps is immediately cleaned with heparinized saline solution in the ultrasonic cleaner. The guide tube is flushed and its position changed slightly so that the next biopsy specimen will not be taken in the identical location. If it is necessary to reassess the location of the guide tube with reference to the endocardium, another small injection of contrast medium is made. If the guide tube becomes grossly dislocated, the inner catheter with or without a guide wire may be reinserted to aid its manipulation to the area of choice again. The forceps is then reinserted and the next sample taken. After three specimens have been obtained from the right ventricle, the guide tube is withdrawn to the inferior vena cava and the procedure is repeated for the left ventricle by way of the femoral artery. If it has been anticipated that the left ventricle may be entered more readily by way of the foramen ovale from the inferior vena cava, a catheter-guide tube set will have been prepared in advance, molded to measure for that route in the specific patient.

Results

In the first 10 patients in whom the technique was used, a diagnostic right and left heart catheterization was performed immediately before the biopsy. Particular attention was paid to injections into the right and left ventricles and the aortic root, the former to quantitate ventricular function and provide orientation for the biopsy, the latter to rule out an anomalous coronary artery. Table I presents summary data on these patients. With few exceptions the hearts were very large. Specimens were obtained from both ventricles in 8 of the 10 hearts. There was a minor complication in Patient 8, who had hypertrophic cardiomyopathy. This patient's left ventricle was very active and repeatedly ejected the guide tube, so that repeated efforts were needed to reposition it. More than average amounts of aspiration and flushing were needed, and a small blood transfusion was given after the procedure. Although blood is necessary after some diagnostic catheterizations in infants and children, it would not have been needed in this case if biopsy had not been done.

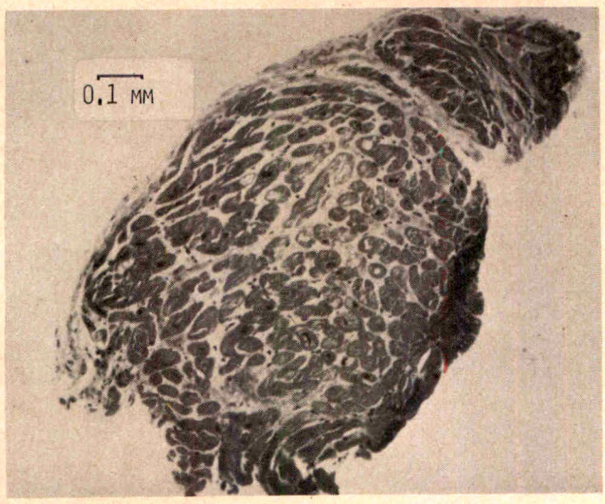

FIGURE 4. Section at widest diameters of a specimen obtained with a no. 5F forceps, showing normal thin endocardium at upper left (×90, reduced by 34 percent).

Complications: Although severely affected patients were included in the group, none had a biopsy-related complication, except for the anemia noted in Patient 8. One or two premature ventricular contractions occurred in each patient at the moment the specimens were taken. No other changes in the electrocardiogram were noted in any patient either during the procedure or within a 48 hour follow-up period.

Ten days after the biopsy and 8 days after discharge from the hospital Patient 5 died suddenly. This child had extremely severe cardiomyopathy with a cardiothoracic ratio of 0.8. Death was due to her disease, and the postmortem examination exonerated the biopsy. Although three specimens had been taken from each ventricle, no gross or microscopic evidence of the biopsy sites could be found, nor was there any suggestion that thrombosis or embolism had occurred. Thus a serendipitous autopsy confirmed the triviality of the injury produced by a small sharp biopsy forceps applied with a light touch.

The time required to take six specimens averaged about 1 hour. Little additional fluoroscopic time was needed unless there were unusual anatomic problems (Table I). There were no vascular complications.

Biopsy specimens: Figure 4 shows a specimen obtained with a no. 5F forceps. This forceps has the same size jaws and yields the same size specimens as most of those currently used in adults in this country and Great Britain.[2–5] The no. 4F forceps yields proportionately smaller samples (Fig. 3), but because it is used in younger infants with smaller myocardial cells the quantity of pathologic information per bite is not much reduced.

The detailed pathologic and virologic results in these first 10 cases are presented in other papers.[6,7] To date these few biopsies have yielded some hitherto unreported information on cardiomyopathy and endocardial fibroelastosis and helped in the genetic counseling of a family.

Discussion

The first transvascular myocardial biopsy technique was devised by Sakakibara and Konno[8] in 1962. They and their colleagues have studied with a record of great safety more than 800 patients of all ages including some infants (personal letter from Ds. Sekiguchi, Konno and Takao to P.R.L.). Few young children outside of Japan have been subjected to myocardial biopsy, mainly because their technique, which was not specifically designed for infants, has certain disadvantages: (1) The stiffness of their biopsy catheter requires that it be inserted into the carotid artery to permit biopsy of a child's left ventricle or into the jugular vein for biopsy of the right ventricle. (2) Cutdown on the vessel is required because of the large caliber of the instrument. (3) Cleaning the biopsy catheter to remove all blood between uses is extremely difficult. (4) Vessels, valves and the myocardium can be traumatized by the free passage of the instrument in the circulatory system.[9]

Advantages and experimental trials of the technique: In the early 1970's, reports of transvascular myocardial biopsy began to appear in the United States and England.[2,3] Richardson's bioptome[4] is a bronchoscopic biopsy forceps clothed with thin plastic that he introduced by a percutaneous entry sheath and manipulated freely into the right or the left ventricle. Our technique uses a similar forceps without the plastic; thus it is much smaller and more suitable for pediatric application and is easily cleansed ultrasonically. The need for some means of guiding the biopsy forceps to the site was shown in experiments in this laboratory on large dogs; considerable difficulty of manipulation was evident and the aorta was perforated in one animal. The type of guide tube used differs from that suggested by Brooksby et al.[5] because it is "molded to measure" for the specific patient. This requirement was established by experiments with small dogs in which unshaped guide tubes tended to fold where the curves were sharp. Finally, in a series of trials on rabbits weighing approximately 3 kg, a special softer shafted forceps was found essential for small subjects.

The sheath material from which the guide tubes are fashioned is ideal for the purpose. It has just the right degree of elasticity and "memory" and sufficient radiopacity to permit exact visualization of the positions of the end of the tube, the forceps and the endocardium so that an endocardial electrode is unnecessary and specimens can be obtained with minimal pressure against the endocardium. In small dogs, specimens were obtained using light pressure and a sharp forceps without leaving a discernible trace when the heart was examined at autopsy 7 days later. On the other hand, when a dull forceps or heavy pressure was used intentionally, full thickness damage of the myocardium occurred.

Clinical applications: Although a human neonate has not yet presented with clinical findings justifying biopsy, well tolerated transaortic biopsy of the left ventricle in 20 rabbits in this laboratory established the feasibility and safety of performing a biopsy of the heart

of a full-term human newborn. Such an infant would normally have a heart at least three times larger than the rabbit hearts studied. How many specimens might be or need be obtained is not known; the limit of three from each side is arbitrary. It has not usually led to inordinate blood loss or prolongation of the procedure and has caused no evident trauma even in rabbits.

We believe that transvascular endomyocardial biopsy can be performed with safety and convenience in infants and young children with the technique presented. Whether the procedure becomes widely accepted may depend on confirmation that early biopsy helps in advancing the diagnosis, nosology and general understanding of the cardiomyopathies.

References

1. **Takahashi M, Petry EL, Lurie PR, et al:** Percutaneous heart catheterization in infants and children. I. Catheter placement and manipulation with guide wires. Circulation 42:1037–1048, 1970
2. **Ali N, Ferrans VJ, Roberts WC, et al:** Clinical evaluation of transvenous catheter technique for endomyocardial biopsy. Chest 63:399–402, 1973
3. **Caves PK, Schultz WP, Dong E, et al:** New instrument for transvenous cardiac biopsy. Am J Cardiol 33:264–267, 1974
4. **Richardson PJ:** Kings' endomyocardial bioptome. Lancet 1:660–661, 1974
5. **Brooksby IAB, Swanton RH, Jenkins BS, et al:** Long sheath technique for introduction of catheter tip manometer or endomyocardial bioptome into left or right heart. Br Heart J 36:908–912, 1974
6. **Neustein HB, Fujita M, Lurie PR:** Transvascular endomyocardial biopsy in infants and children: myocardial findings in ten cases of cardiomyopathy. Hum Pathol, in press
7. **Neustein HB, Lurie PR, Fujita M:** Transvascular endomyocardial biopsy in children: endocardial fibroelastosis. Arch Pathol, in press.
8. **Sakakibara S, Konno S:** Endomyocardial biopsy. Jpn Heart J 3: 537–542, 1962
9. **Wennemark JR, Sommers HM, Zitnik RS:** Endomyocardial biopsy, experimental study with a catheter technique. Am Heart J 72: 675–680, 1966

Life Expectancy Without Surgery in Tetralogy of Fallot

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All published autopsy cases of patients with tetralogy of Fallot who died without surgical treatment were studied to determine the life expectancy of such persons. In addition, the data from a study of persons with tetralogy alive in Denmark in 1949 were reanalyzed. The survival data from these two sources were remarkably similar, indicating that 66 percent of persons with tetralogy of Fallot not treated surgically live to age 1 year, 49 percent to age 3 years and 24 percent to age 10 years; thereafter, the hazard function (or instantaneous risk of death) remains constant. The chance of survival is significantly less when pulmonary atresia, rather than stenosis, is present.

Surgical treatment is indicated for most patients with tetralogy of Fallot and is usually effective. However, several questions remain unanswered, including how many infants with tetralogy should be treated surgically and whether patients with tetralogy who survive into the third and fourth decades of life require an operation. Data on life expectancy and other aspects of the natural history of persons with tetralogy of Fallot are required to answer these questions.

Randomized studies of the length of life with and without surgical treatment in patients with tetralogy of Fallot are not now possible. Therefore, we analyzed published clinical and autopsy data to estimate the life expectancy of persons with tetralogy who were not treated surgically.

Material and Methods

The 1949 Danish study: The material for our study came from two sources. The first was from Rygg et al.,[1] who determined the ages of all persons with tetralogy of Fallot alive in Denmark in 1949. That year was chosen because until 1949 no person in Denmark had had corrective surgery for tetralogy of Fallot. Fifty-four of the 216 persons with tetralogy had had palliative operations in 1948 and 1949, and 5 had died at operation. Most of these 54 patients were older than age 6 years and all were older than age 2 years at operation. For the purposes of the study, all 54 patients were considered to be alive at the end of 1949. The number of births in Denmark in each of the 58 previous years was known. It was assumed in the study that each year tetralogy of Fallot was present in 0.4 of every 1,000 live births. From these data the number of persons born with tetralogy of Fallot who were alive in 1949 at ages 1 to 59 years was calculated and their length of life estimated.

Published autopsy cases: Our second source of data was reported autopsy cases of tetralogy of Fallot. Most cases included were reviewed individually in their original publication to determine whether the diagnosis was in fact tetralogy of Fallot, whether the age at death was known and, as far as possible, whether the death was related to the presence of the malformation. However, some data from reliable sources were presented as "grouped" information (for example, "10 cases dying between ages 1 to 10 years"), and thus the individual cases could not be examined. In 54 cases sufficient data were presented to indicate that the

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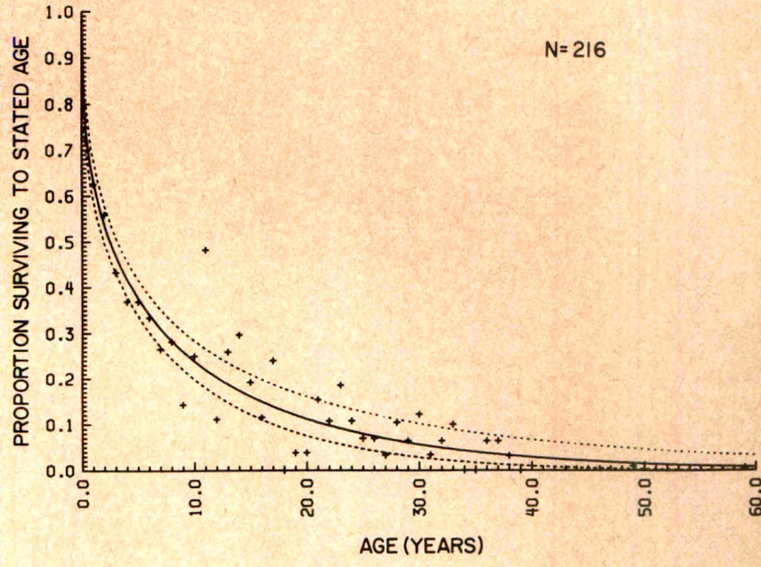


FIGURE 1. Life expectancy of persons with tetralogy of Fallot, based on data from the Danish population study. **Crosses** represent data points calculated in that study. The **solid line** (with its 70 percent confidence limits enclosed by the **dashed lines**) represents parametric analysis of the data, which resulted in the equation (single hit model[19]): Probability of dying = $[1 - \exp(\mu t/m)]^m$, where exp is e, the base of the natural logarithms; $\mu = \exp(\beta)$ where $\beta = -6.2 \pm 0.25$; t is age on January 1, 1950 in months and $m = 0.36 \pm 0.056$. Significance levels of coefficients, $P_\beta < 0.0001$ and $P_m < 0.0001$; correlation between coefficients, $r = 0.976$. The results are shown to age 60 years. N = number of patients.

diagnosis was tetralogy of Fallot with pulmonary atresia.[2–8] In 195 cases sufficient data were found to indicate that the diagnosis was tetralogy of Fallot without pulmonary atresia.[2–4,6,9–13] These cases, in addition to 317 cases in which the presence or absence of pulmonary atresia could not be determined, constitute the total group of 566 autopsy cases.[2–17*] The autopsy cases were analyzed to determine survival or life expectancy data, that is, the cumulative number of cases in which the age at death was greater than a series of ages, t.

Survival curves of cases with pulmonary stenosis versus atresia: The survival data in cases without pulmonary atresia appeared more favorable in the early years of life than current clinical experience suggests. Most of the 195 cases in this group were reported by persons and institutions known to care for few if any small children. Furthermore, when the 195 cases without and the 54 cases with pulmonary atresia are removed from the total group of 566 cases, the survival data of the remaining cases are much less favorable than the data from the total group. This suggests that the 195 patients removed were a particularly favored subset among those without pulmonary atresia. Also, if these data are correct, mathematical analysis of the combined curve indicates that 60 percent of the patients at any age had pulmonary atresia, which is highly unlikely. Because these data appeared unreliable, we looked for another method of determining the life expectancy of persons with tetralogy of Fallot but without pulmonary atresia. Knowing the survival data for persons with pulmonary atresia, assuming a 33 percent incidence rate of

* The specific case numbers in each publication and the original source for each case in review series are available from the authors.

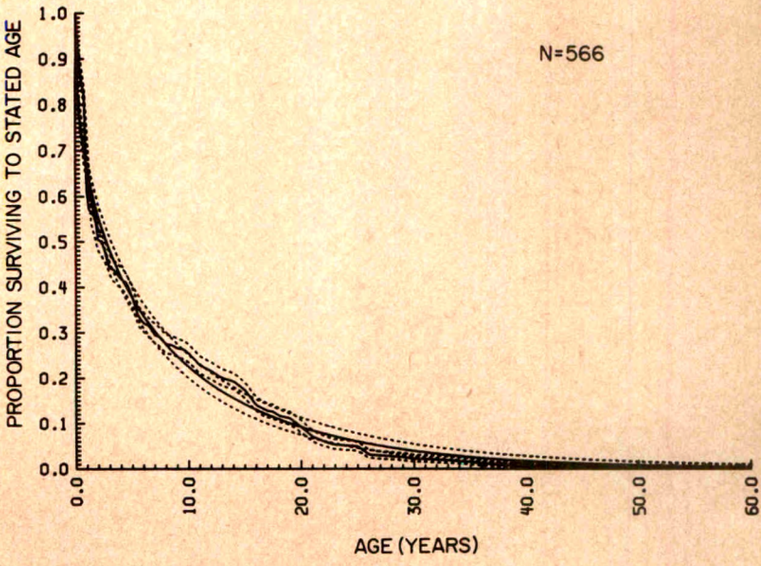
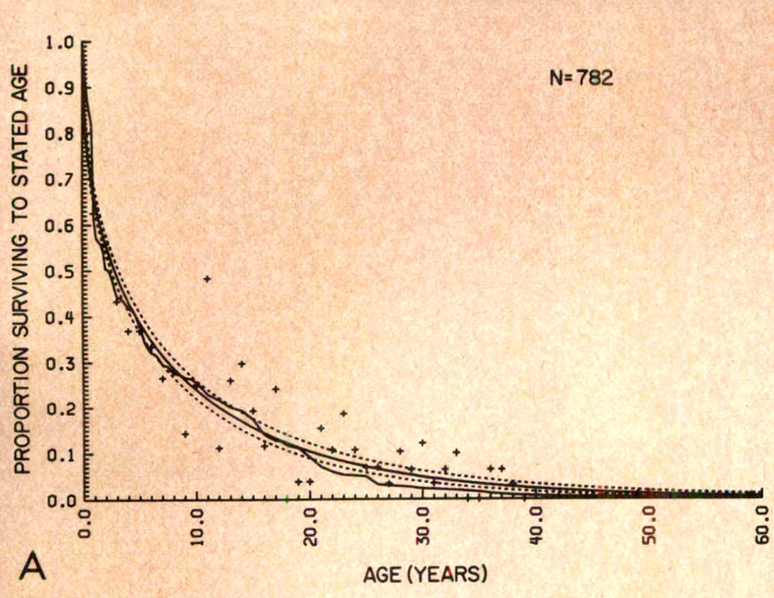
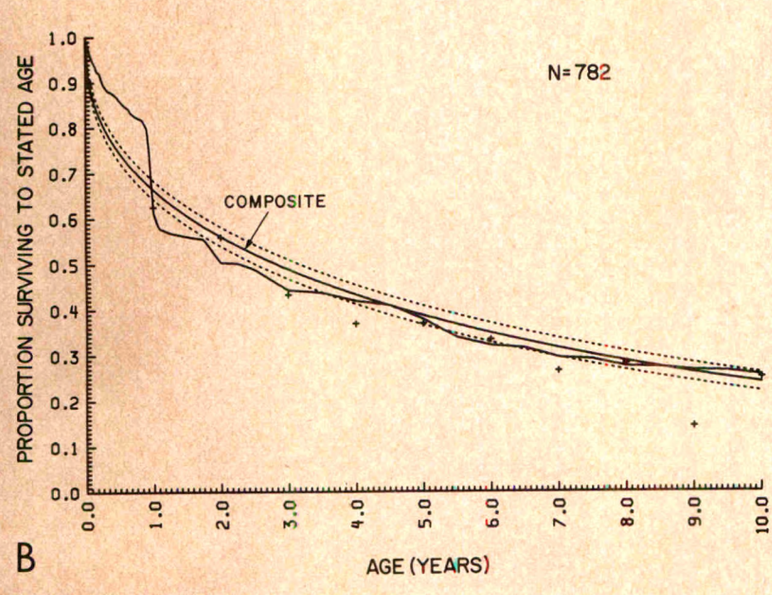


FIGURE 2. Life expectancy of persons with tetralogy of Fallot, based on autopsy study.[2–17] The **jagged line** (with its 70 percent confidence limits enclosed by the **dashed lines**) represents the data from the nonparametric actuarial analysis. The **smooth line** (with its 70 percent confidence limits) represents the parametric analysis, which yielded the same equation as in Figure 1, with the coefficients $\beta = -5.87 \pm 0.081$ and $m = 0.425 \pm 0.0178$. Significance level of the coefficients, $P_\beta < 0.0001$ and $P_m < 0.0001$; correlation between coefficients: $r = 0.500$. N = number of patients.





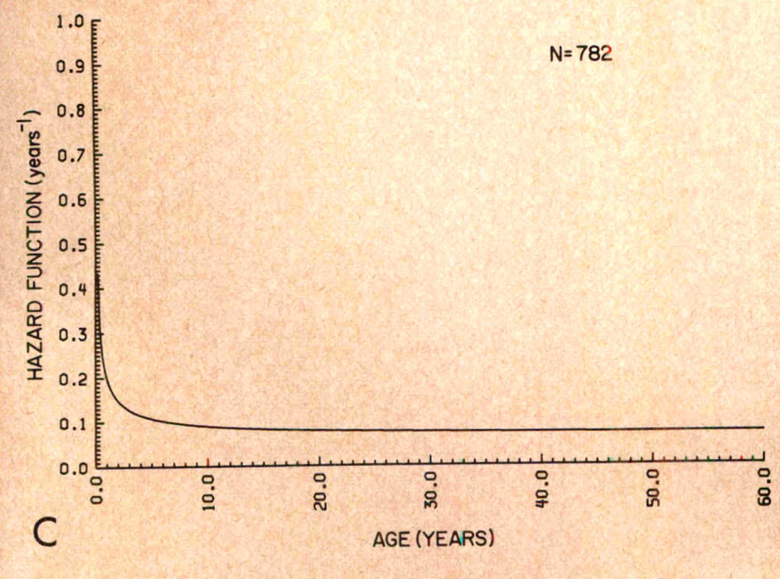


FIGURE 3. Life expectancy of persons with tetralogy of Fallot, based on combined analysis of the Danish data and autopsy data. **A,** results to age 60 years; **B,** results to age 10 years on an expanded time scale; **C,** proportion of persons at risk of dying each year (hazard function), according to the age of the person. The greatest risk is in the first year of life. The actual data points (**crosses**) calculated in the Danish study are shown, as is the nonparametric actuarial analysis (**jagged line**) from the autopsy data. The smooth line (with its 70 percent confidence limits enclosed by the **dashed lines**) results from a combined parametric analysis that yielded the same equation as in Figure 1 with the coefficients, $\beta = -6.00 \pm 0.072$ and $m = 0.410 \pm 0.0172$. Significance level of the coefficients, $P_\beta < 0.0001$ and $P_m < 0.0001$; correlation between coefficients, $r = 0.809$.

congenital pulmonary atresia among 566 autopsy cases of tetralogy of Fallot and knowing the survival data for the total group, we derived survival curves for those presumed to have pulmonary stenosis (PS) rather than atresia (PA) as follows:

$$S_{CA}(t) = S_{PA}(t) + (1 - \alpha)S_{PS}(t) \quad (1)$$

where $S_{CA}(t)$ = survival curve for 566 composite autopsy (CA) cases; $S_{PA}(t)$ = survival curve for 54 cases of tetralogy of Fallot with pulmonary atresia; $S_{PS}(t)$ = generated survival curve for tetralogy of Fallot with pulmonary stenosis rather than pulmonary atresia; and $\alpha = 0.33$, the assumed incidence rate of pulmonary atresia at birth among patients with tetralogy of Fallot. Thus, the survival curve for the composite group is assumed to consist of the sum of the two separate survival curves proportionate to their respective incidence rates at birth. $S_{PS}(t)$ is derived by rearranging equation 1 algebraically.

Statistical methods: Nonparametric descriptions of the autopsy series were made using the product-limit method of Kaplan and Meier.[18] We modified their method to take into account the data from individual case reports as well as grouped data from which individual ages at death could not be determined (Hazelrig JB, Turner ME Jr, Blackstone EH, in preparation). Parametric estimates of survival (applicable to both the autopsy data and the Danish data) were calculated using the family of "survival equations" described by Turner and Pruitt.[19] The data were fitted to the "survival" equation using the method of maximal likelihood suggested by Gross and Clark[20] and a nonlinear optimization program developed by Hazelrig et al.[21] The specific survival equation selected from the family of equations was the one that did not fit the data significantly worse than the "generic" equation.

The parametric analysis yielded formulas that could be directly manipulated to generate the hazard function $\lambda(t)$, which is the instantaneous death rate:

$$\lambda(t) = -S'(t)/S(t) \quad (2)$$

where $S'(t)$ is the slope (first derivative) of the survival function $S(t)$. The formulas were also manipulated to generate the survival function for tetralogy of Fallot with pulmonary stenosis rather than pulmonary atresia, as described. The confidence limits for this calculated curve were computed from the variance (Var) estimated by the equation:

$$\mathrm{Var}[S_{CA}(t)] = \alpha^2\mathrm{Var}[S_{PA}(t)] + (1 - \alpha)^2\mathrm{Var}[S_{PS}(t)] \quad (3)$$

because $S_{PA}(t)$ and $S_{PS}(t)$ are independent. By algebraic manipulation, $\mathrm{Var}[S_{PS}(t)]$ could be computed.* The hazard function can be converted to a percent risk per year for a constant hazard rate by the formula $100 \times (1 - \exp[-\lambda])$, where exp is the base of the natural logarithms.

Results

The Danish study: According to the parametric analysis of the Danish study, 64 percent of patients born with tetralogy of Fallot, including those with pulmonary atresia, are alive at age 1 year, 54 percent at 2 years, 47 percent at 3 years and 24 percent at age 10 years (Fig. 1). The hazard function (or the instantaneous risk of death at any given age) is highest in the first year of life, gradually declines until age 10 years and remains essentially constant at about a 6.4 percent risk per year thereafter. Related to this is continual decrease in the number of survivors, so that only 11 percent of persons born with tetralogy of Fallot are alive at age 20 years, 6 percent at 30 years and 3 percent at 40 years.

Composite autopsy series: Parametric analysis of the composite autopsy data (566 cases) indicates that 66 percent of patients born with tetralogy of Fallot, including those with pulmonary atresia, are alive at age 1 year, 56 percent at 2 years, 48 percent at 3 years and 22 percent at age 10 years (Fig. 2). The hazard function is similar to that derived from the Danish study.

Combined series: Combined parametric analysis of the data from the Danish study and from autopsy reports (782 cases) is permissible because the survival function for the two series was not significantly different ($P = 0.2$). The combined analysis indicates that 66 percent of patients born with tetralogy of Fallot are alive at age 1 year, 56 percent at 2 years, 49 percent at 3 years and 24 percent at age 10 years (Fig. 3, A and B). The combined hazard function remains constant after age 10 years (Fig. 3C).

Tetralogy of Fallot with pulmonary atresia: The life expectancy of patients with tetralogy of Fallot and pulmonary atresia (54 cases) is shorter, according to the autopsy data (Fig. 4, A and B). By parametric analysis only 66 percent of patients are alive at age 6 months, 50 percent at 1 year, 33 percent at 2 years, 25 percent at 3 years and 8 percent at age 10 years. The 70 percent confidence limits are wider than in the previous analyses because of the smaller number of cases. The hazard function is very high in the first few years of life (Fig. 4C).

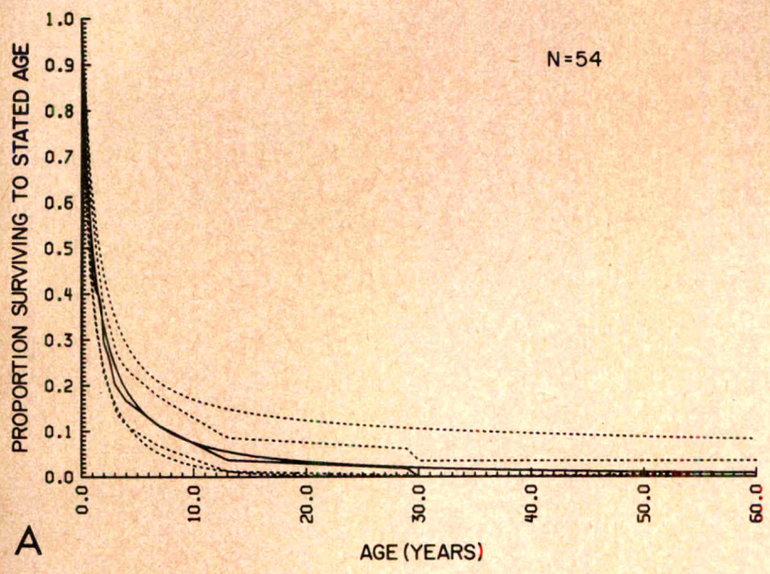
Tetralogy of Fallot without pulmonary atresia: The data from the autopsy study for all persons with tetralogy of Fallot known to be without pulmonary atresia (195 cases) are shown in Figure 5. The derived data (see Material and Methods) for persons with tetralogy of Fallot without pulmonary atresia are shown in Figure 6. The differences between the curves from the 195 cases and those from the derived data are largely in the first few years of life. The derived parametric analyses indicate that 75 percent of patients are alive at age 1 year, 60 percent at 3 years and 30 percent at age 10 years.

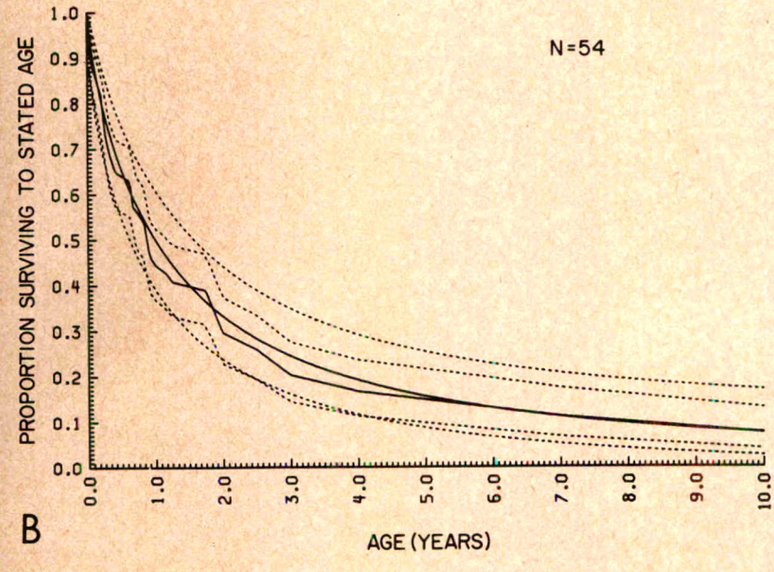
For completeness and ease of reference, the curves for persons with tetralogy of Fallot and those known to have pulmonary atresia and the *derived* curves for those without pulmonary atresia are shown in Figure 7. In general, persons with pulmonary atresia have the shortest life, and those with pulmonary stenosis have a better prognosis. The confidence limits of all survival curves overlap in the older age group, suggesting that there may be no significant differences among older patients in the three groups. In addition, the confidence limits of all curves overlap in the first 3 months of life.

Discussion

Evaluation of methods and their possible limitations: The Danish study assumed that 0.4 instances of the tetralogy of Fallot occurred in each 1,000 live births, and other studies[22–25] indicate that this assumption is reasonable. The similarity of the results in

* We are indebted to Dr. Edwin Bradley of the Department of Biostatistics for the development of these relations.





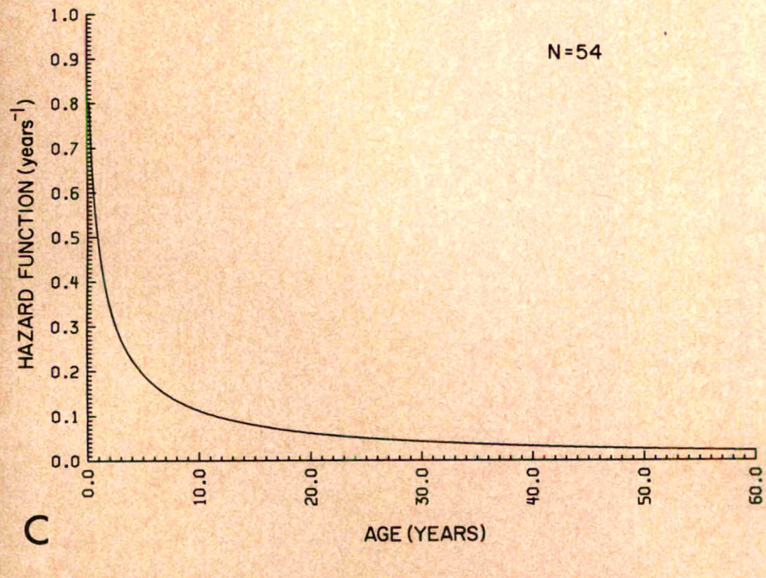


FIGURE 4. Life expectancy of persons with tetralogy of Fallot and known pulmonary atresia, based on autopsy data. The portrayal in **A, B** and **C** is as in Figure 3. The smooth line represents the equation (positive generic model[19]): Probability of dying = $[1 - (1 + \mu t/m\nu)^{-\nu}]^m$, where (as in Fig. 2) $\beta = -3.3 \pm 0.85$, t is age in months, $m = 0.7 \pm 0.22$ and $\nu = 1.4 \pm 0.80$. Significance level of coefficients: $P_\beta = 0.0003$, $P_m = 0.0001$ and $P_\nu = 0.09$ (chi square test for single hit model being different from this generic model, $P = 0.006$); correlation between coefficients, $r_{\beta,m} = -0.938$, $r_{\beta,\nu} = -0.697$ and $r_{m,\nu} = 0.558$. N = number of patients.

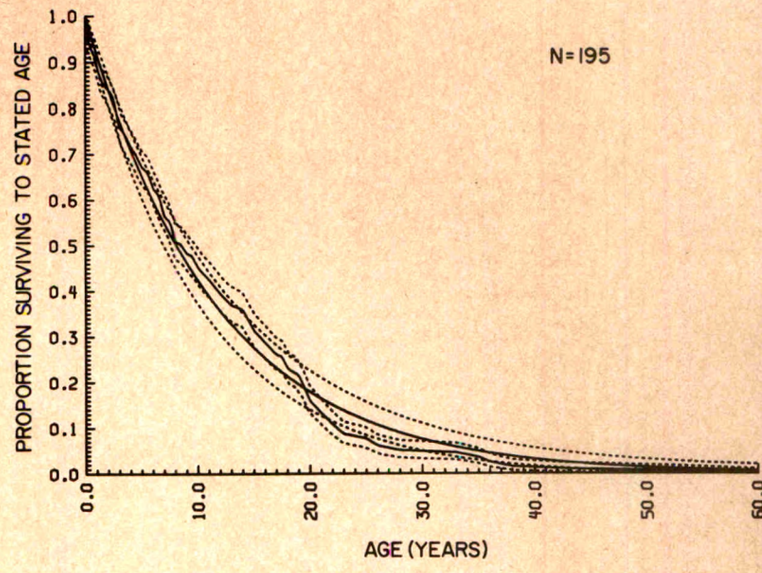


FIGURE 5. Life expectancy of persons with tetralogy of Fallot and known pulmonary **stenosis** (not atresia), based on autopsy data from 195 patients. The smooth line represents the equation: Probability of dying = $1 - \exp(-\mu t)$, where exp is e, the base of the natural logarithms; $\mu = \exp(\beta)$, where $\beta = -4.94 \pm 0.082$, and t is age in months. Significance level of coefficient, $P_\beta < 0.0001$. The **jagged line** represents the nonparametric actuarial analysis. N = number of patients.

the Danish study and in the composite autopsy study indicates that the cases in the latter are probably an adequate sample of persons born with tetralogy of Fallot.

The assumption that 33 percent of persons with tetralogy of Fallot have congenital pulmonary atresia is based on four reports indicating that this proportion is 27, 42, 39 and 35 percent, respectively.[14,22,26,27] This estimate is consistent with the recent experience of Arciniegas, who found 26 patients (22 percent) with tetralogy of Fallot and pulmonary atresia among the 118 patients with tetralogy on whom he operated in infancy (personal communication).

The nonparametric actuarial method used in the analyses is standard for handling this type of data, except for the important modification for grouped information. The method has several limitations. No interpolation scheme between data points at individual events or projection of confidence limits is theoretically admissible even when the actual data seem to follow a simple, smoothly decreasing pattern; in addition, confidence limits should widen as patients are withdrawn because of unknown status. A major weakness exists in handling a large number of patients "lost to follow-up" or "withdrawn alive," as in the Danish cross-sectional study for which no "actuarial" estimate is possible, in part because no events (deaths) were recorded. The theoretical binomial limits to any actuarial method in such cases are usually extraordinarily broad and may render any nonparametric method of little

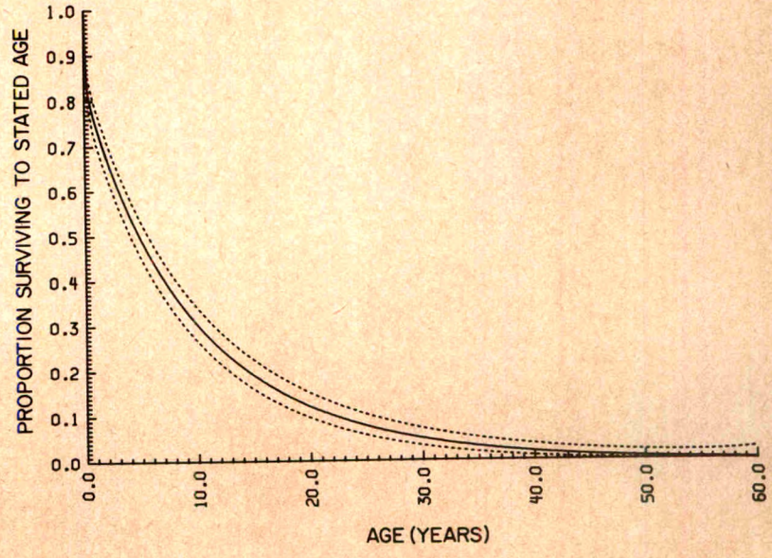
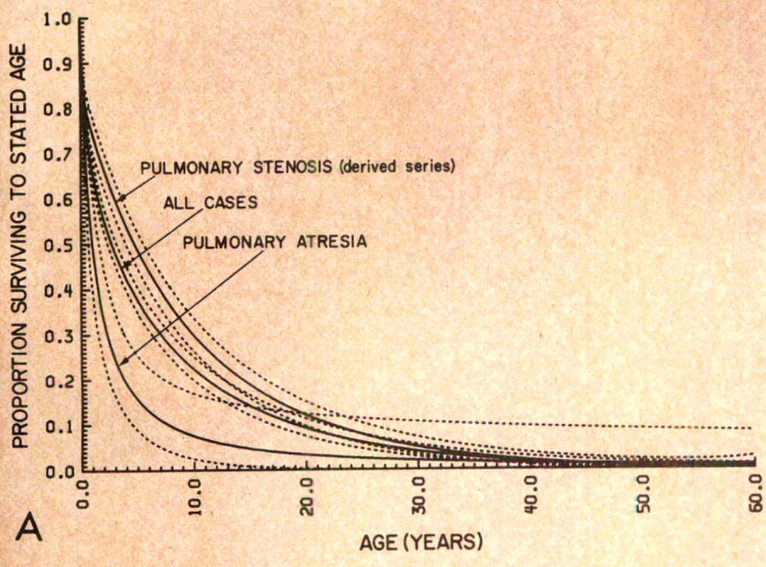
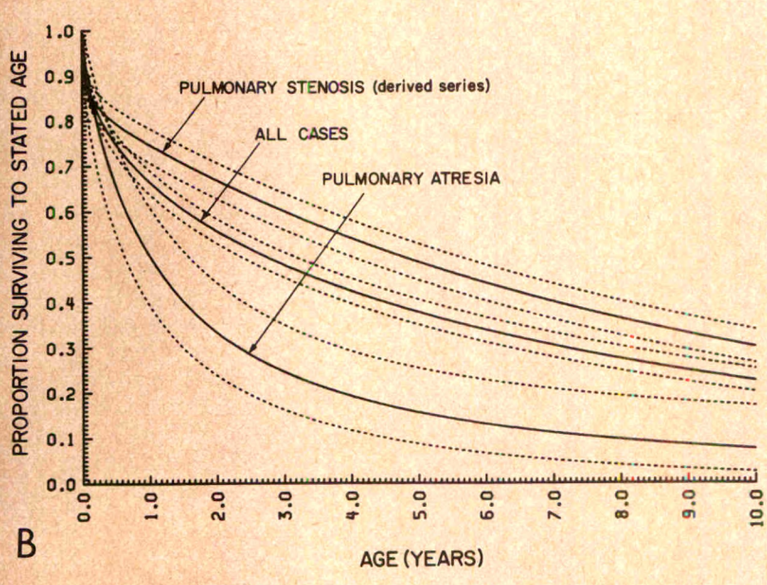


FIGURE 6. Life expectancy of persons with tetralogy of Fallot without pulmonary atresia, derived as described in Methods.





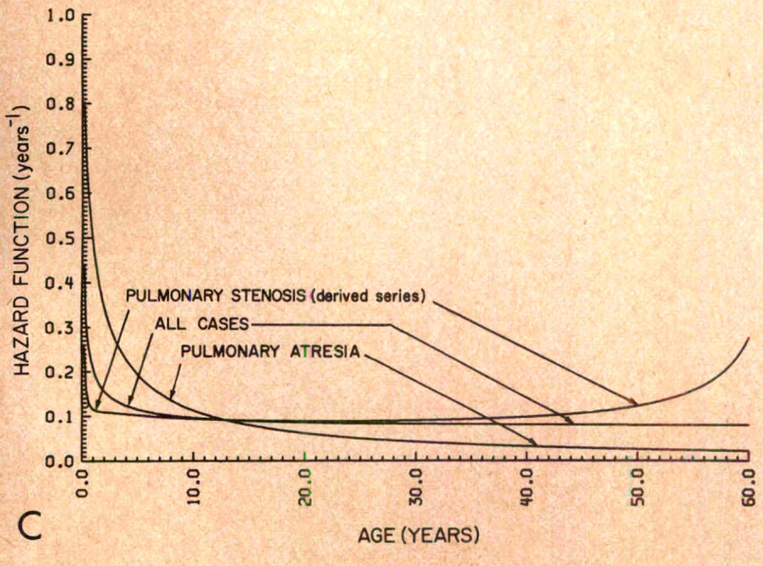


FIGURE 7. Combination of parametric equations from Figures 3, 4 and 6. The presentations in **A, B** and **C** are as in Figure 3.

value. Serial correlation of the actuarial estimates may produce errors throughout the calculated life table; the grouped data were especially troublesome in this regard, generating estimates that were at times outside the theoretical binomial limits.

The parametric technique overcomes these disadvantages by generating continuous estimates at all ages (as expected of any regression equation of low order); by treating "unknown" data as if they followed the expected survivorship curve for the known data, thereby allowing us to combine longitudinal information (autopsy series) with cross-sectional information (Danish series), which, as far as we know, has not previously been possible; and by treating individual events independently. In addition, the advantages of expressing a survivorship function as a simple formula have been recognized for many years, particularly in reports on industrial reliability.[20,28] With this method, the hazard function is easily calculated and provides insight into the changing risk among survivors. In addition, regression coefficients of different series can be compared so that statistical differences are easily determined, and the formulas can be manipulated to generate such useful functions as "surgical salvage," given the data on natural history and surgical risk. The *scheme* used in parametric analysis is unique in that a particular formula for the survivorship function is not assumed at the outset, but instead a flexible, high-order "generic" model is first fitted and then simplified, if possible, to one of the many formulas in the family of equations derived from the generic model.

Definition and material: We intended to include all persons with a morphologic diagnosis of tetralogy of Fallot—that is, all those with atrioventricular (A-V) concordant connection and a large ventricular septal defect in the left ventricular outflow tract immediately beneath the aortic valve, biventricular origin of the aorta, origin of the pulmonary artery from right ventricle and pulmonary stenosis that was at least partly infundibular and severe enough to produce marked right ventricular hypertrophy. Pulmonary atresia, when present, was pulmonary truncal, valvular, infundibular or valvular and infundibular, and the remnant of the pulmonary artery was above the right ventricle. The ventricular septal defect was subpulmonary in some cases. No case with complete A-V canal was included. We attempted to exclude cases with absent left and right pulmonary arteries, so-called truncus arteriosus type IV.[29]

We presume that the survival curves we derived for persons who have pulmonary atresia are applicable prognostically to persons who have atresia in the first few months of life, and that those derived for persons with pulmonary stenosis rather than atresia are applicable to persons who have tetralogy of Fallot with pulmonary stenosis in the first few months of life, whether or not they are cyanotic at that time or manifest pulmonary atresia later in life. The clinician must refine the prognostic prediction for an individual patient from these curves on the basis of severity of the patient's cyanosis and thus of the pulmonary stenosis.

We included in the autopsy group only patients believed to have died of causes related to their malformation. If the patient was known to have died of an unrelated cause such as tuberculosis or typhoid fever, the cause was excluded so that the survival data would be applicable at the present time.

Evaluation of role of severity of pulmonary stenosis in survival: The life expectancy of the group of patients with tetralogy of Fallot from the autopsy study is strikingly similar to that derived from the Danish study, in which a completely different study technique was used. This finding strongly suggests that both studies correctly predict the life expectancy of persons with tetralogy.

The data support the generally accepted concept that the natural history of persons born with tetralogy of Fallot is determined primarily by the severity of the pulmonary stenosis, as demonstrated by the tendency of persons with pulmonary atresia to die at a younger age than those without pulmonary atresia or the group as a whole. The infants with pulmonary atresia who die in the early months of life probably lack large discrete "bronchial" collateral arteries and die as a result of gradual spontaneous closure of the patent ductus arteriosus, which Bharati et al.[30] found in 81 percent of cases. Large "bronchial arteries" or, less commonly, large discrete paramediastinal vessels or coronary-pulmonary artery fistulas,[31] are present in many of the patients with tetralogy of Fallot and congenital pulmonary atresia (38 of 80 surgical cases in the experience of Alfieri et al.[32]) and do not close spontaneously. Although these vessels often allow the infant to survive the early months of life, the collateral pulmonary flow they provide is frequently insufficient to prevent arterial desaturation and cyanosis. Thus, many such patients die in childhood. Those who reach the third decade of life have a large collateral pulmonary blood flow and probably as a result are at that age at less risk of dying at any given time than persons with classic tetralogy of Fallot without pulmonary atresia.

In the subset of persons with tetralogy of Fallot and pulmonary stenosis, the pulmonary stenosis usually becomes more severe with time and results in increasing arterial desaturation, cyanosis, polycythemia and, ultimately death, usually from hypoxia, pulmonary thromboses or cerebral thromboses or abscesses. In patients surviving into the fourth and fifth decades of life, congestive heart failure may cause death.

Therapeutic implications: Because about one half of surgically untreated patients with tetralogy of Fallot die in the first 2 years of life, surgical programs for persons with this malformation must include techniques for surgical intervention in the early months and years of life. Also, because the hazard function does not decrease in the third to fifth decades of life, the person with tetralogy in this age group is still subject to the risks of the malformation.

Institutions reporting that less than half of their patients treated surgically for tetralogy of Fallot are younger than 2 years of age may be delaying surgical intervention unwisely or may have a patient population that represents less than the full spectrum of cases of tetralogy of Fallot.

References

1. **Rygg IH, Olesen K, Boesen I:** The life history of tetralogy of Fallot. Dan Med Bull 18:Suppl II:25–30, 1971
2. **Bauer DDeF, Astbury EC:** Congenital cardiac disease: bibliography of the 1,000 cases analyzed in Maude Abbott's atlas with an index. Am Heart J 27:688–723, 1944
3. **Burke EC:** The Anatomic Basis for Pulmonary Stenosis in the Tetralogy of Fallot. Thesis, Graduate School, University of Minnesota, 1951 p 1–41
4. **Donzelot E, D'Allaines F, Dubost Ch, et al:** Déductions chirurgicales tirées de l'étude de 54 pieces anatomiques de tetralogie de Fallot. Sem Hop Paris 28:877–897, 1952
5. **Edwards JE, Carey LS, Neufeld HN, et al:** Congenital Heart Disease: Correlation of Pathologic Anatomy and Angiocardiography. Philadelphia and London, WB Saunders, 1965, p 458–471
6. **Keith A:** Malformations of the heart. Lancet 2:359–363, 1909
7. **Meiring DR:** A case of multiple congenital cardiac defect with sudden death. Clin Proc 5:207–212, 1946
8. **Miskall EW:** The tetralogy of Fallot. Report of an unusual case. JAMA 128:803–804, 1945
9. **Fallot A:** Contribution a l'anatomie pathologique de la Maladie bleue (cyanose cardiaque). Marseille Medicale 25:138–158, 1888
10. **Fallot A:** Contribution a l'anatomie pathologique de la Maladie bleue (cyanose cardiaque). Marseille Medicale 25:341–354, 1888
11. **Lev M, Strauss S:** Stenosis of the infundibulum. Arch Intern Med 70:53–60, 1942
12. **Feigin I, Rosenthal J:** The tetralogy of Fallot. Am Heart J 26: 302–312, 1943
13. **Sidenberg SS, Kessler MM, Wolpaw R:** A case of tetralogy of Fallot with absence of cerebellar vermis; termination by brain abscess. J Pediatr 23:719–728, 1946
14. **Keith JD, Rowe RD, Vlad P:** Heart Disease in Infancy and Childhood, second edition. New York, Macmillan, 1967, p 598–643
15. **Rygg IH, Bertelsen S, Borgeskov S, et al:** The palliative surgical treatment of tetralogy of Fallot. Dan Med Bull 18:Suppl II:59–80, 1971
16. **Ferencz C:** The pulmonary vascular bed in tetralogy of Fallot. I. Changes associated with pulmonic stenosis. Bull Johns Hopkins Hosp 106:81–99, 1960
17. **Kusumoto M:** Natural history of tetralogy of Fallot. J Tokyo Women's Med Coll 38:337–344, 1968
18. **Kaplan EL, Meier P:** Non-parametric estimation from incomplete observations. J Am Stat Assoc 53:457–482, 1958
19. **Turner ME Jr, Pruitt KM:** A common basis for survival, growth, and autocatalysis. Math Biosci 39:113–123, 1978
20. **Gross AJ, Clark VA:** Survival Distributions: Reliability Applications in the Biomedical Sciences. New York, John Wiley and Sons, 1975, p 204–220
21. **Hazelrig JB, Turner ME, Jr, Ackerman E:** A function minimization computer package (MFIT) for nonlinear parameter estimation providing readily accessible maximum likelihood estimates. Comput Biomed Res 11:51–64, 1978
22. **Carlgren LE:** The incidence of congenital heart disease in children born in Gothenburg 1941–1950. Br Heart J 21:40–50, 1959
23. **Nadas AS, Fyler DC, Castaneda AR:** The critically ill infant with congenital heart disease. Mod Concepts Cardiovasc Dis 42:53–58, 1973
24. **Willunsen ÅL:** Environmental Factors in Congenital Malformations. Copenhagen, FADLs Forlag, 1970
25. **Richards MR, Merritt KK, Samuels MH, et al:** Congenital malformations of the cardiovascular system in a series of 6,053 infants. Pediatrics 15:12–29, 1955
26. **Rowe RD, Vlad P:** Diagnostic problems in the newborn. In, Heart Disease in infancy (Barratt-Boyes BG, Neutze JM, Harris EA, ed). Baltimore, Williams & Wilkins, 1973, p 3–22
27. **Sherman FE:** An Atlas of Congenital Heart Disease. Baltimore, Lea & Febiger, 1963, p 187–195
28. **Buckland WR:** Statistical Assessment of the Life Characteristic. New York, Hafner, 1964, p 11–73
29. **Collett RW, Edwards JE:** Persistent truncus arteriosus: a classification according to anatomic types. Surg Clin North Am 29: 1245–1270, 1949
30. **Bharati S, Paul MH, Idriss FS, et al:** The surgical anatomy of pulmonary atresia with ventricular septal defect: pseudotruncus. J Thorac Cardiovasc Surg 69:713–721, 1975
31. **Krongrad E, Ritter DG, Hawe A, et al:** Pulmonary atresia or severe stenosis and coronary artery-to-pulmonary artery fistula. Circulation 46:1005–1011, 1972
32. **Alfieri O, Blackstone EH, Kirklin JW, et al:** Surgical treatment of tetralogy of Fallot with pulmonary atresia. J Thorac Cariovasc Surg, in press

Association of Interrupted Aortic Arch With Malformations Producing Reduced Blood Flow to the Fourth Aortic Arches

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Interrupted aortic arch is a rare congenital malformation of the great arteries with loss of continuity between the proximal portion of the aortic arch and the descending aorta, which is usually supplied by a patent ductus arteriosus. The hearts of 12 patients with interrupted aortic arch listed in the autopsy files of The Johns Hopkins Hospital were evaluated. Four categories were identified. Seven hearts with normal outflow tract relations had significant pulmonary arterial override of a ventricular septal defect and thus received part of left ventricular and all of right ventricular ejection flow; flow into the aorta was correspondingly reduced. Two hearts had mitral valve obstruction with decreased left heart flow. Two hearts had double inlet left ventricle and transposed great arteries with the aorta originating from a small anterior conal chamber. One heart had a truncus malformation with a disproportionately large flow entering the pulmonary arterial division. In each of these hearts, the pattern of the outflow tracts and associated malformations suggested that there was a preferential flow of blood into the sixth arches and correspondingly a reduced flow into the fourth arches at the time of normal disappearance of components of the embryonic aortic arch system. Thus, interrupted aortic arch may simply be disappearance of the normally persisting connection between the left fourth and sixth arches as a result of flow imbalance in early cardiogenesis.

Interrupted aortic arch is a rare congenital malformation of the great arteries that involves loss of continuity between the proximal portion of the aorta and its descending portion. The descending aorta is then supplied by a patent ductus arteriosus or, in rare cases, entirely from collateral circulation. The pattern of origin of the aortic arch vessels varies, but usually the interruption occurs either distal to the left subclavian artery or between the left carotid and left subclavian arteries.[1] Previous studies have suggested that embryonic hemodynamics may account for both normal[2] and abnormal[3–6] cardiogenesis. In this study the hearts of patients with interrupted aortic arch subjected to autopsy at The Johns Hopkins Hospital were evaluated for associated malformations. The results suggest that interrupted aortic arch is associated with malformations of the heart and great arteries that would produce a reduced blood flow to the embryonic fourth aortic arches.

Observations

Case material: Patients listed in the autopsy files of The Johns Hopkins Hospital were included in this study if (1) the heart was available for review; (2) no intracardiac surgical procedure had been performed; and (3) interrupted aortic arch was present. The 12 patients in the series are listed in Table I. They ranged in age from 2 days to 7 weeks; 7 were female (clinical data were not available for one patient). The 12 hearts could be classified into four groups: 7 with normally formed atrioventricular (A-V) valves and a significant pulmonary arterial ov-

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TABLE I

Associated Malformations in 12 Autopsy Cases of Interrupted Aortic Arch

Case no.	Age (days)	Race and Sex	Venous Return	Inter-Atrial Septum	A-V Valves	IVS	Semi-lunar Valves	Over-ride of PA Over VSD	Ductus Arteriosus	Arch Vessels From Descend-ing Aorta
Normal A-V Valves and Pulmonary Arterial Override										
1	3	BF	...	PFO	...	VSD	...	70%	PDA	LSC
2	10	WF	...	PFO	...	VSD	...	50%	PDA	None
3	?	?	...	PFO	...	VSD	BAV	50%	PDA	?
4	2	BF	...	PFO	...	VSD	BAV	50%	PDA	None
5	4	WM	...	PFO	...	VSD	BAV	50%	PDA	LSC
6	3	WM	...	PFO	...	VSD	BAV	30%	PDA	LSC
7	3	BF	PLSVC	PPFO	...	VSD	BAV	30%	PDA	RSC, LSC
Mitral Valve Obstruction and Normally Related Great Vessels										
8	49	WM	...	PFO	MS	VSD	BAV	0%	PDA	LSC
9	45	BF	PLSVC	PFO	MA	VSD	BAV, BPV	0%	PDA	RSC, LSC
Double Inlet Left Ventricle and Transposition of Great Vessels										
10	7	WM	...	PPFO	DILV	VSD	TX	...	PDA	None
11	22	BF	...	PFO	DILV	VSD	TX	...	PDA	None
Normal A-V Valves and Truncus Arteriosus										
12	22	WF	...	PFO	...	VSD	Truncus	...	PDA	RSC, LSC

A-V = atrioventricular; BAV = bicuspid aortic valve; BPV = bicuspid pulmonic valve; DILV = double inlet left ventricle; IVS = interventricular septum; LSC = left subclavian artery; MA = mitral atresia; MS = mitral stenosis; PDA = patent ductus arteriosus; PFO = patent foramen ovale; PLSVC = persistent left superior vena cava; PPFO = probe patent foramen ovale; RSC = right subclavian artery; TX = transposition; VSD = ventricular septal defect.

erride over the ventricular septal defect, 2 with significant mitral valve obstruction but normally formed outflow tracts, 2 with double inlet left ventricle and transposition of the great arteries and 1 with truncus arteriosus malformation. All 12 had some communication across the interatrial septum (2 with a flap-guarded, and 10 with a nonflap-guarded patent foramen ovale); all had a communication across the interventricular septum, and all had a patent ductus arteriosus feeding the descending aorta. In all cases the ascending aorta not only was smaller than the corresponding pulmonary artery, but also was smaller in caliber than would be expected in a patient of that size.

Pulmonary override: In this group (Cases 1 to 7) the A-V valves were normal and the great arteries were normally oriented. However, each had a subpulmonary ventricular septal defect (six in the membranous position, one intramuscular), with 30 to 70 percent override of the pulmonary artery over the left ventricle (Fig. 1). Five had a bicuspid aortic valve, and in each the missing commissure was the one adjacent to the pulmonary valve (juxtapulmonary position). In Cases 1 through 5, the missing commissure was represented by a residual raphe representing the remnant of the original separation of the outflow tract cushions. In Cases 6 and 7, no raphe was observed.

Mitral valve obstruction: Two hearts (Cases 8 and 9) had significant obstruction of the mitral valve (mitral stenosis and mitral atresia, respectively) and normal orientation of the great arteries. Both had a disproportionately small left ventricle ("left heart syndrome"). Both ventricular septal defects were in the membranous position, but the pulmonary artery did not override the defect. In both hearts the aortic valve was bicuspid with juxtapulmonary raphes, and in Case 8, there was also a bicuspid pulmonary valve with a juxtaaortic raphe.

Double inlet left ventricle and transposition: Two hearts manifested double inlet left ventricle, transposition of the great arteries and an interventricular communication. The atrioventricular (A-V) and semilunar valves were normally formed. It was not meaningful to assess the pulmonary arterial override in these hearts because, as is typical for this paired defect, the pulmonary artery arose from an enlarged left ventricle whereas the aorta arose from a rudimentary anterior conal chamber (Fig. 2).

Truncus malformation: A single heart (Case 12) had a truncus malformation, with a normally formed quadricuspid valve and a subvalve interventricular communication. The A-V valves were normally formed. The subsequent pattern of outflow tract separation past the common truncal vessel suggested a relatively increased flow through the pulmonary portion. The ascending aorta was less than half the diameter of the main pulmonary artery and gave rise only to the carotid arteries. The much larger main pulmonary artery gave rise to

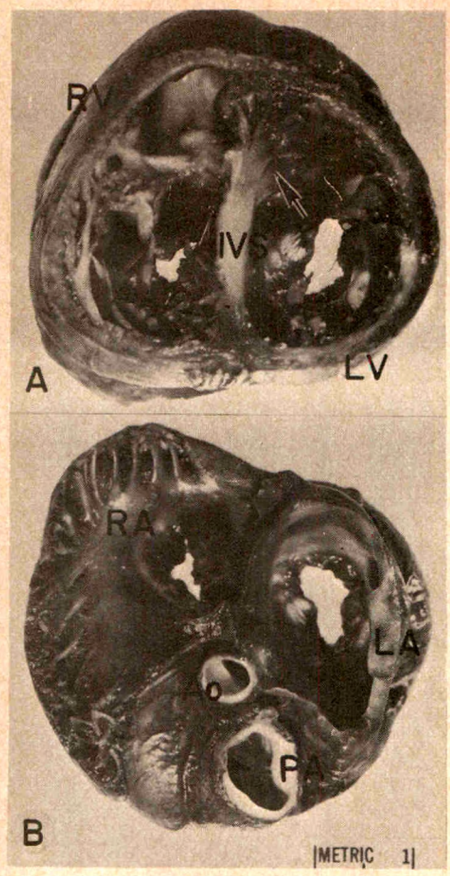

FIGURE 1. Case 1. Base of the heart as viewed from the apical aspect **(A)** and from the atrial aspect **(B).** Approximately 70 percent of the pulmonary artery (PA) overrides the ventricular septal defect **(arrow),** and thus receives flow from the left ventricle (LV). There is a consequent disproportion of the caliber of the aorta (Ao) and pulmonary artery. The atrioventricular and semilunar valves are normal. IVS = interventricular septum; LA = left atrium; RA = right atrium; RV = right ventricle.

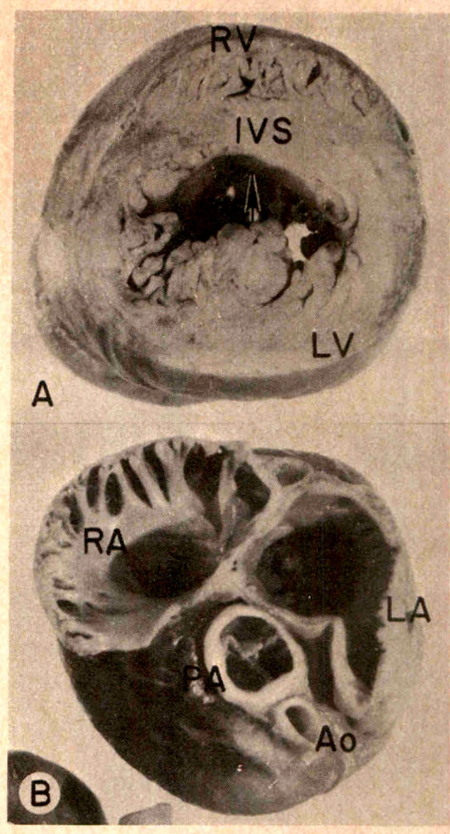

FIGURE 2. Case 11. Base of the heart depicted and labeled as in Figure 1. There is double inlet left ventricle (LV) with the two atrioventricular valves entering the posteriorly positioned left ventricle. The great vessels are transposed, with the aorta (Ao) arising from the anteriorly positioned conal chamber of the right ventricle (RV). The interventricular septum (IVS) has approximately a 90° rotation from its usual position, and blood entering the right ventricle must cross the interventricular communication **(arrow).** The semilunar valves are normal and the relative size of the great vessels reflects the proportions of flow through them. Abbreviations as in Figure 1.

both right and left pulmonary arteries and connected by way of a patent ductus arteriosus to the descending aorta, from which both subclavian arteries arose.

Discussion

In this study, the hearts of 12 patients with interrupted aortic arch were examined for associated malformations of the heart and great arteries. This case series joins about 200 other cases now reported. With rare exceptions[1,7] the defect is found in association with other major cardiovascular abnormalities.[8] Typically, there is an interventricular communication and patency of the ductus arteriosus, through which flow passes into the descending aorta. Aortic valve abnormalities and left heart syndrome are also commonly observed. Our case series includes as well two less commonly observed associations: transposition of the great arteries[9] and truncus malformation.[10] Can we interpret interrupted aortic arch as a secondary feature in the setting in which these other lesions develop?

Development of semilunar valves and great arteries to differential ventricular flow: Previous studies have related normal development of the semilunar valves and great arteries to the differential flow of blood from the two ventricular chambers.[2,4] These chambers, which begin to separate at stage 14, may be responsible for a major revision of the heart, through formation of separated ejection streams. The direction of outflow from the right ventricle produces early selection of the left sixth arterial arch, whereas the left ventricular ejection stream flows equally into both fourth arterial arches (Fig. 3). The mesenchyme downstream from the cardiac tube, which invests these preferred arterial channels of flow, represents the so-called aortic-pulmonary septum.[11] Rather than a dis-

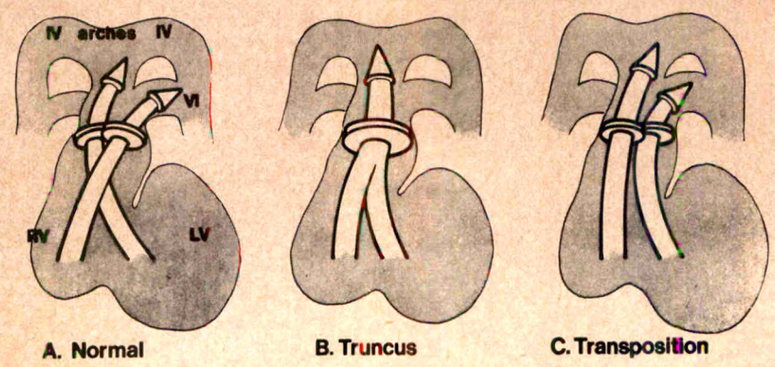

FIGURE 3. Diagrammatic representation of the outflow tract relations in the normal stage 14 embryo **(A)** and as postulated for truncus malformation **(B)** and transposition of the great vessels **(C).** In the normal embryo at this stage, the left sixth arch has already been selected, whereas the fourth arches remain symmetric. LV = left ventricle; RV = right ventricle.

tinct structure which actively divides the aortic sac into two great arteries, this "septum" appears to be mesenchyme filling in the space between two paths of blood flow. The left fourth arch then develops at the expense of the right because of decreased resistance to flow on the left, resulting from its connection through the dorsal aorta to the left sixth arch.

In transposition of the great arteries, it has been postulated that the *right* ventricular outflow stream is directed more anteriorly and superiorly than normal and thus enters and "selects" the *left fourth* arch as its preferred channel of flow (Fig. 3). The posterior outflow tract of the *left* ventricle then enters the *left sixth arch* and preferentially flows to the left because the left dorsal aorta has been enlarged by the right ventricular outflow.[4] The key to both this mechanism and that for normal development of the great arteries is the observation from normal embryogenesis that asymmetry of the right ventricular outflow stream precedes asymmetry of the left ventricular outflow stream by two stages (14 and 16, respectively). Thus only one component of maldirected flow is required to explain the full set of outflow connections in transposition. In truncus arteriosus malformation, the left and right ventricular

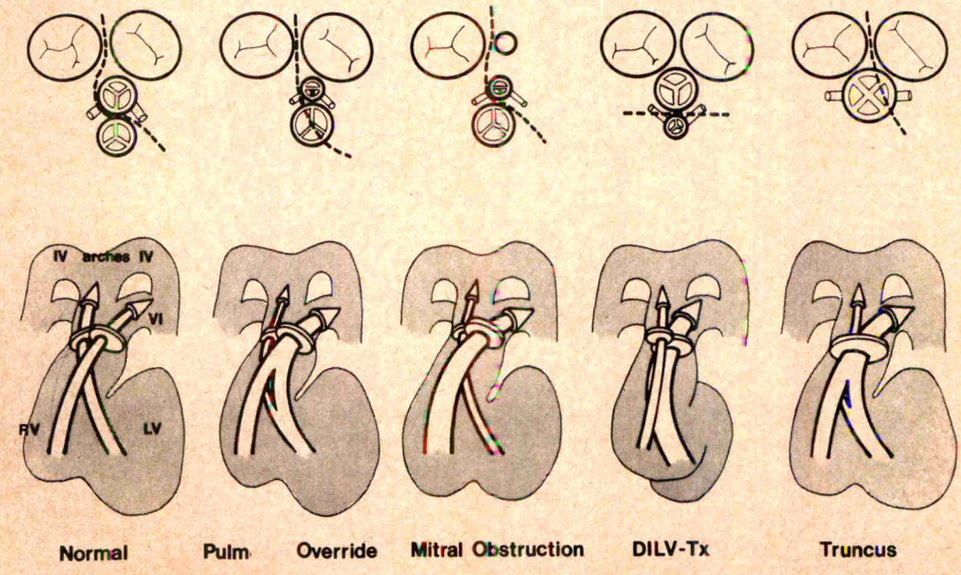

FIGURE 4. Diagrammatic representation of the atrioventricular valve and outflow tract relations in the normal heart, and in the four groups with interruption of the aortic arch. DILV-Tx = double inlet left ventricle with transposition of the great vessels; LV = left ventricle; Pulm = pulmonary; RV = right ventricle.

outflow streams may be directed so that the streams *intersect* at the level of the developing semilunar valves, resulting in a single outflow entering the *left fourth arch.*[12]

Hemodynamic basis of interrupted aortic arch: Because normal development of the embryo involves the disappearance of aortic arch vessels on the basis of differential hemodynamics, it has been suggested that interrupted aortic arch may have a hemodynamic basis as well.[3] Several of our findings may have particular significance with regard to such pathologic hemodynamics. First is the presence of some form of interventricular communication in all 12 hearts. In the single heart with truncus malformation and the two with double inlet left ventricle, this was the obligate interventricular communication associated with these defects. In the two groups with normally related great arteries, either the left ventricle emptied a reduced proportion of its stroke volume into the aorta because of a significant pulmonary arterial override over the ventricular septal defect, or there was no pulmonary arterial override but total left ventricular stroke volume was reduced because of mitral valve obstruction (Fig. 4). Likewise, in the two hearts with double inlet left ventricle and transposition of the great arteries, the rudimentary *right* ventricle ejected a reduced flow into the aorta because both A-V valves emptied directly into the *left* ventricle. Finally, if truncus malformation is considered an incomplete separation of the proximal left and right ventricular ejection streams,[12] again the single heart in our series with this pattern showed relatively decreased flow into the aortic parts of the truncus. The interventricular septum normally closes in stage 18, but its patency may persist when a significant flow across the septum is maintained.[6] The four structural patterns in our series are all consistent with blood flow across the interventricular septum and preferential flow into the left sixth aortic arch.

The vessels of the embryonic aortic arch normally develop an elastic lamina at approximately stage 17. After this time, it is unlikely that segments of these vessels can simply drop out entirely, as is the case in interrupted aortic arch, although the relative caliber of these vessels may be markedly altered by differential flow patterns.[13] This suggests that ventricular outflow already has a well established pattern of decreased flow into the left fourth aortic arch, leading to interruption of the aortic arch before stage 17. The exact point of interruption depends on variations in this flow.[3] The rare cases, noted clinically, without a ventricular septal defect or patent ductus arteriosus[1,7] are not inconsistent with this interpretation. The early establishment of the flow pattern in the arch vessels could permit subsequent normal intracardiac development. Acquisition of collateral channels to fill the descending aorta would permit closure of the ductus as occurs in coarctation of the aorta. Association of aorticopulmonary window, double outlet right ventricle or corrected transposition of the great arteries with interrupted aortic arch[14] would also not be inconsistent with the imbalanced flow pathogenesis suggested for this anomaly.

Aortic valve abnormalities in interrupted aortic arch: An important feature of our series is that every abnormally formed aortic valve (Cases 3 through 9) had its deformed (raphe present) or absent (raphe absent) commissure in the juxtapulmonary position. Likewise, the single heart with both a bicuspid aortic valve and a bicuspid pulmonary valve had both a juxtapulmonary and a juxtaaortic raphe, respectively. Normal semilunar valves develop during stages 15 through 17 at the downstream end of the embryonic cardiac tube by remodeling of the endocardial cushion material.[2] Two valves, each with three commissures, form by subdivision of the two larger of the four endocardial cushions. Thus there is consistent occurrence of the valve abnormalities at the site of separation between the two larger cushions, an obligate commissure.

Maintained patency of interventricular septum: The endocardial cushion material in the outflow tract initially forms normally. With the preferential flow into the sixth arch the pulmonary component of the subdivision of the outflow tract at the semilunar valve level is probably larger than the aortic. In these cases the absent commissure or raphe in the smaller aortic valve was always found in the juxtapulmonary position, a circumstance that can be explained by an aortic-ward displacement of the mesenchymal septum that forms around the outflow streams distal to the cardiac tube and that divides the endocardial cushions. This same preferential flow pattern out the sixth aortic arch causes a crossover between the left and right ventricles and thus may maintain the patency of the interventricular septum in stage 18. Patent foramen ovale and patent ductus arteriosus, normally present in the newborn, persist in most patients because of left to right ventricular shunts secondary to aortic obstruction.

References

1. **Pillsbury RC, Lower RR, Shumway NE:** Atresia of the aortic arch. Circulation 30:749–754, 1964
2. **Maron BJ, Hutchins GM:** The development of the semilunar valves in the human heart. Am J Pathol 74:331–344, 1974
3. **Celoria GC, Patton RB:** Congenital absence of the aortic arch. Am Heart J 58:407–413, 1959
4. **DeVries PA, Saunders JBCM:** Development of the ventricles and spiral outflow tract in the human heart: a contribution to the development of the human heart from age group IX to age group XV. Contrib Embryol Carnegie Inst Wash 37:87–114, 1962
5. **Hutchins GM:** Coarctation of the aorta explained as a branch point of the ductus arteriosus. Am J Pathol 63:203–214, 1971
6. **Winn KJ, Hutchins GM:** The pathogenesis of tetralogy of Fallot. Am J Pathol 73:157–172, 1973
7. **Morgan JR, Forker AD, Fosburg RG, et al:** Interruption of the aortic arch without a patent ductus arteriosus. Circulation 42:961–965,

1970
8. **Everts-Suárez EA, Carson CP:** The triad of congenital absence of aortic arch (isthmus aortae), patent ductus arteriosus and interventricular septal defect—a triology. Ann Surg 150:153–159, 1959
9. **Hamburger LP Jr:** Congenital cardiac malformation presenting complete interruption of the isthmus aortae with transposition of the great arteries. Bull Johns Hopkins Hosp 61:421–428, 1937
10. **Roberts WC, Morrow AG, Braunwald E:** Complete interruption of the aortic arch. Circulation 26:39–59, 1962
11. **Kramer TC:** The partitioning of the truncus and conus and the formation of the membranous portion of the interventricular septum in the human heart. Am J Anat 71:343–370, 1942
12. **Maron BJ, Hutchins GM:** Truncus arteriosus malformation in a human embryo. Am J Anat 134:167–174, 1972
13. **Rodbard S:** Vascular caliber. Cardiology 60:4–49, 1975
14. **Van Praagh R, Bernhard WF, Rosenthal A, et al:** Interrupted aortic arch: surgical treatment. Am J Cardiol 27:200–211, 1971

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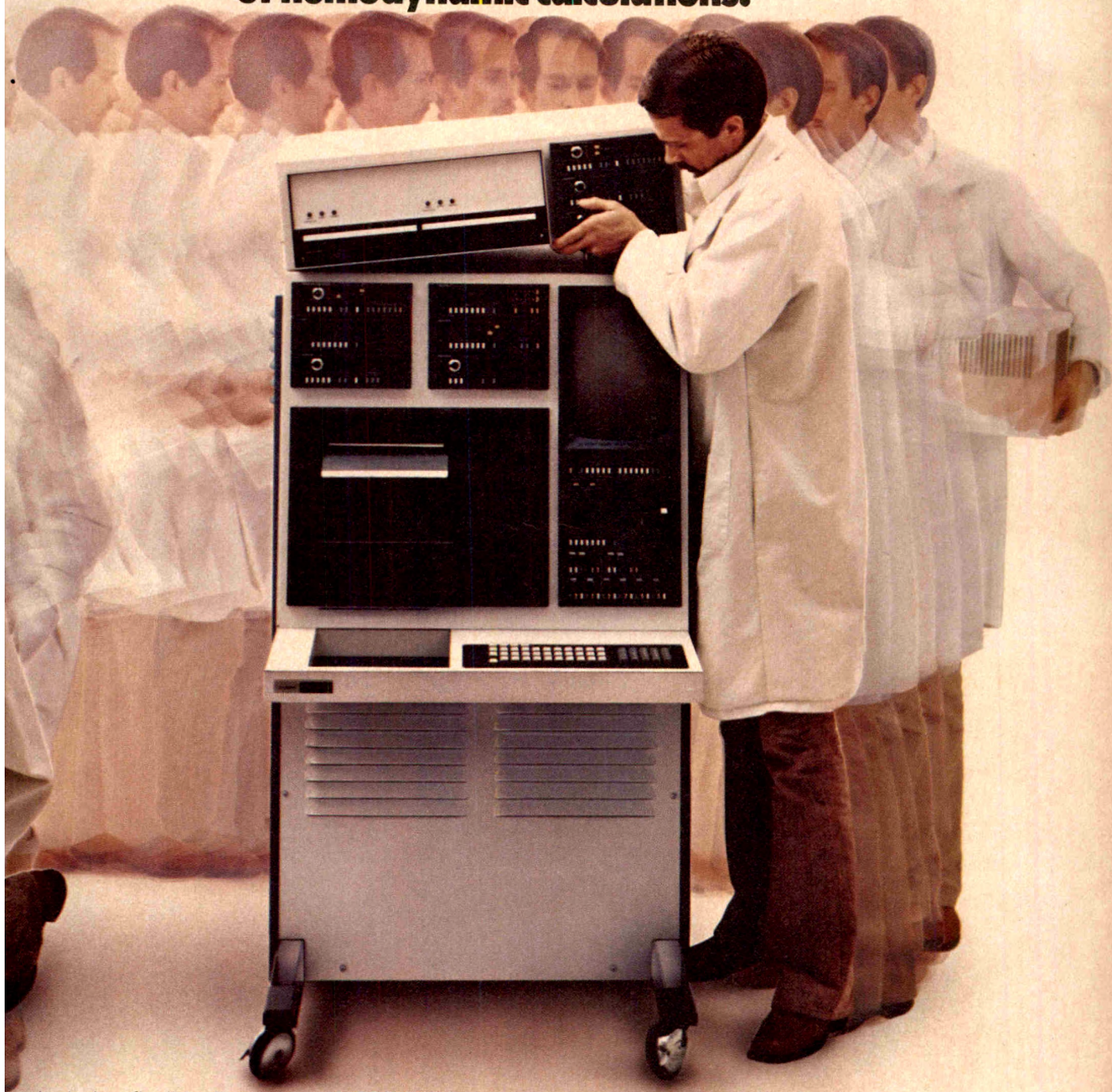

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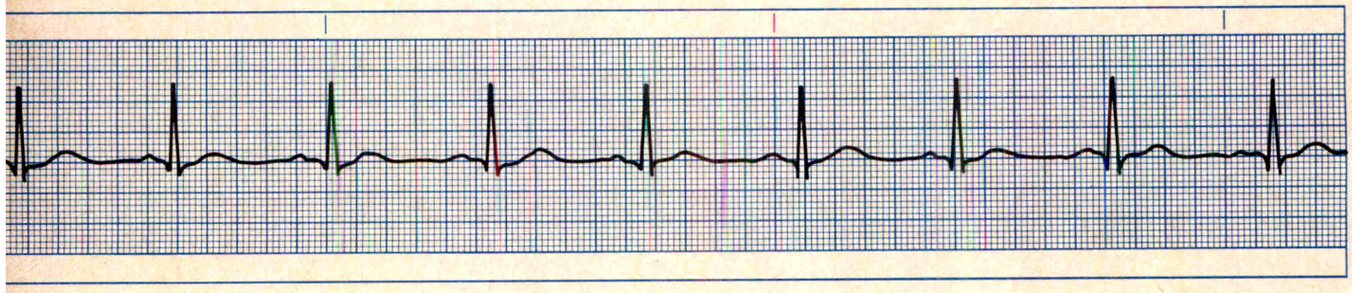

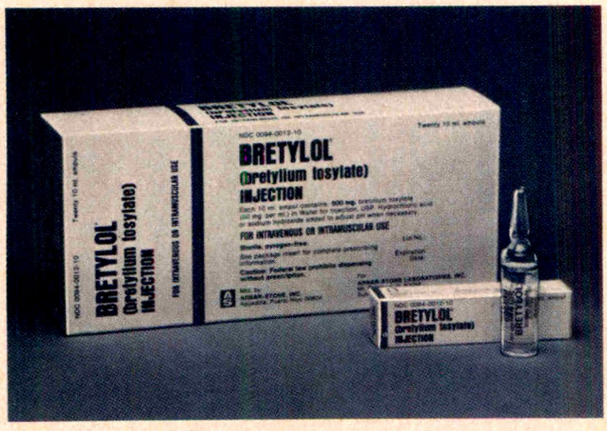

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Clinical Studies

1. Holder, Douglas A., Sniderman, Allan D., Fraser, D. George and Fallen, Ernest. Experience with bretylium tosylate by a hospital cardiac arrest team. *Circulation. 55*:541-544, 1977.

2. Bernstein, Jerrold G. and Koch-Weser, Jan. Effectiveness of bretylium tosylate against refractory ventricular arrhythmias. *Circulation. 45*:1024-1034, 1972.

3. Cohen, H.C., Gozo, E.G., Langendorf, R., Kaplan, B.M., Chan, A., Pick, A. and Glick, G. Response of resistant ventricular tachycardia to bretylium. *Circulation. 47*:331-340, 1973.

4. Bacaner, Marvin B. Treatment of ventricular fibrillation and other acute arrhythmias with bretylium tosylate. *Am. J. Cardiol. 21*:530-543, 1968.

5. Chatterjee, Kanu, Mandel, William J., Vyden, John K., Parmley, William W. and Forrester, James S. Cardiovascular effects of bretylium tosylate in acute myocardial infarction. *JAMA. 223*:757-760, 1973.

6. Terry, G., Vellani, C.W., Higgins, M.R. and Doig, A. Bretylium tosylate in treatment of refractory ventricular arrhythmias complicating myocardial infarction. *Brit. Heart J. 32*:21-25, 1970.

7. Dhurandhar, R.W., Teasdale, S.J. and Mahon, W.A. Bretylium tosylate in the management of refractory ventricular fibrillation. *Can. Med. Assoc. J. 105*:161-166, 1971.

8. Cooper, Jerome A. and Frieden, Julian. Appraisal and reappraisal of cardiac therapy: bretylium tosylate. *Am. Heart J. 82*:703-706, 1971.

9. Sanna, Gianpietro and Arcidiacono, Raffaele. Chemical ventricular defibrillation of the human heart with bretylium tosylate. *Am. J. Cardiol. 32*:982-987, 1973.

Pharmacology Studies

10. Bigger, J.T. and Jaffe, C.C. The effect of bretylium tosylate on the electrophysiologic properties of ventricular muscle and Purkinje fibers. *Am. J. Cardiol. 27*:82-92, 1971.

11. Markis, J.E. and Koch-Weser, J. Characteristics and mechanism of inotropic and chronotropic actions of bretylium tosylate. *J. Pharmacol. Exp. Ther. 178*:94-102, 1971.

12. Wit, A.L., Steiner, C. and Damato, A.N. Electrophysiologic effects of bretylium tosylate on single fibers of the canine specialized conducting system and ventricle. *J. Pharmacol. Exp. Ther. 173*:344-356, 1970.

13. Bacaner, M. Quantitative comparison of bretylium with other antifibrillatory drugs. *Am. J. Cardiol. 21*:504-512, 1968.

14. Bacaner, M.B. and Schrienmachers, D. Bretylium tosylate for suppression of ventricular fibrillation after experimental myocardial infarction. *Nature. 220*:494-496, 1968.

15. Boura, A.L.A. and Green, A.F. The actions of bretylium: adrenergic neuron blocking and other effects. *Br. J. Pharmacol. 14*:536-548, 1959.

16. Hammermeister, K.E., Boerth, R.C. and Warbasse, J.R. The comparative inotropic effects of six clinically used antiarrhythmic agents. *Am. Heart J. 84*:643-652, 1972.

17. Cardinal, Rene and Sasyniuk, Betty I. Electrophysiological effects of bretylium tosylate on subendocardial Purkinje fibers from infarcted canine hearts. *J. Pharmacol. Exp. Ther. 204*:159-174, 1978.

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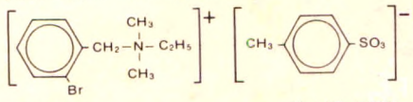

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3. Little effect on the rate of rise or amplitude of the cardiac action potential (Phase 0) or in resting membrane potential (Phase 4) in normal myocardium. However, when cell injury slows the rate of rise, decreases amplitude, and lowers resting membrane potential, BRETYLOL restores these parameters toward normal.

4. Increase in impulse formation and spontaneous firing rate of pacemaker tissue as well as increased ventricular induction velocity.

The restoration of injured myocardial cell electrophysiology toward normal, as well as the increase of the action potential duration and effective refractory period without changing their ratio to each other, may be important factors in suppressing re-entry of aberrant impulses and decreasing induced dispersion of local excitable states.

BRETYLOL induces a chemical sympathectomy-like state which resembles a surgical sympathectomy. Catecholamine stores are not depleted by BRETYLOL, but catecholamine effects on the myocardium and on peripheral vascular resistance are often seen shortly after administration because BRETYLOL causes an early release of norepinephrine from the adrenergic postganglionic nerve terminals. Subsequently, BRETYLOL blocks the release of norepinephrine in response to neuron stimulation. Peripheral adrenergic blockade regularly causes orthostatic hypotension but has less effect on supine blood pressure. The relationship of adrenergic blockade to the antifibrillatory and antiarrhythmic actions of BRETYLOL is not clear. In a study in patients with frequent ventricular premature beats, peak plasma concentration of BRETYLOL and peak hypotensive effects were seen within one hour of intramuscular administration, presumably reflecting adrenergic neuronal blockade. However, suppression of premature ventricular beats was not maximal until 6-9 hours after dosing, when mean plasma concentration had declined to less than one-half of peak level. This suggests a slower mechanism, other than neuronal blockade, was involved in suppression of the arrhythmia. On the other hand, antifibrillatory effects can be seen within minutes of an intravenous injection, suggesting that the effect on the myocardium may occur quite rapidly.

BRETYLOL has a positive inotropic effect on the myocardium, but it is not yet certain whether this effect is direct or is mediated by catecholamine release.

BRETYLOL is eliminated intact by the kidneys. No metabolites have been identified following administration of BRETYLOL in man and laboratory animals. In man, approximately 70 to 80% of a ^{14}C-labelled intramuscular dose is excreted in the urine during the first 24 hours, with an additional 10% excreted over the next three days.

In various studies of BRETYLOL excretion, estimates of the terminal half-life have varied from about 5 to about 10 hours, with an even wider range in individual subjects (4 to 17 hours). Whether this represents true intrapatient variability or limitations of methodology remains to be determined.

Effect on Heart Rate: There is sometimes an initial small increase in heart rate when BRETYLOL is administered, but this is an inconsistent and transient occurrence.

Hemodynamic Effects: Following intravenous administration of 5 mg/kg of BRETYLOL to patients with acute myocardial infarction, there was a mild increase in arterial pressure, followed by a modest decrease, remaining within normal limits throughout. Pulmonary artery pressures, pulmonary capillary wedge pressure, right atrial pressure, cardiac index, stroke volume index, and stroke work index were not significantly changed. These hemodynamic effects were not correlated with antiarrhythmic activity.

Onset of Action: Suppression of ventricular fibrillation is rapid, usually occurring within minutes following intravenous administration. Suppression of ventricular tachycardia and other ventricular arrhythmias develops more slowly, usually 20 minutes to 2 hours after parenteral administration.

INDICATIONS

BRETYLOL is indicated in the treatment of life-threatening ventricular arrhythmias, principally ventricular fibrillation and ventricular tachycardia, that have failed to respond to adequate doses of a first-line antiarrhythmic agent, such as lidocaine or procainamide. At this time, BRETYLOL should not be considered a first-line antiarrhythmic agent.

Use of BRETYLOL should be limited to intensive care units, coronary care units or other facilities where equipment and personnel for constant monitoring of cardiac arrhythmias and blood pressure are available.

Following injection of BRETYLOL, there may be a delay of 20 minutes to 2 hours in the onset of antiarrhythmic action, although it appears to act within minutes in ventricular fibrillation. The delay in effect appears to be longer after intramuscular than after intravenous injection.

CONTRAINDICATIONS

There are no contraindications to use in treatment of ventricular fibrillation or life-threatening refractory ventricular arrhythmias.

WARNINGS

1. Hypotension: Administration of BRETYLOL regularly results in postural hypotension, subjectively recognized by dizziness, light-headedness, vertigo or faintness. Some degree of hypotension is present in about 50% of patients while they are supine. Hypotension may occur at doses lower than those needed to suppress arrhythmias.

> Patients should be kept in the supine position until tolerance to the hypotensive effect of BRETYLOL develops. Tolerance occurs unpredictably but may be present after several days.

Hypotension with supine systolic pressure greater than 75 mm Hg need not be treated unless there are associated symptoms. If supine systolic pressure falls below 75 mm Hg, an infusion of dopamine or norepinephrine may be used to raise blood pressure. When catecholamines are administered, a dilute solution should be employed and blood pressure monitored closely because the pressor effects of the catecholamines are enhanced by BRETYLOL. Volume expansion with blood or plasma and correction of dehydration should be carried out where appropriate.

2. Transient Hypertension and Increased Frequency of Arrhythmias: Due to the initial release of norepinephrine from adrenergic postganglionic nerve terminals by BRETYLOL, transient hypertension or increased frequency of premature ventricular contractions and other arrhythmias may occur in some patients.

3. Caution During Use with Digitalis Glycosides: The initial release of norepinephrine caused by BRETYLOL may aggravate digitalis toxicity. When a life-threatening cardiac arrhythmia occurs in a digitalized patient, BRETYLOL should be used only if the etiology of the arrhythmia appear to be digitalis toxicity and other antiarrhythmic drugs are tive. Simultaneous initiation of therapy with digitalis g and BRETYLOL should be avoided.

4. Patients with Fixed Cardiac Output: In patients with fix output (i.e., severe aortic stenosis or severe pulmonary hy BRETYLOL should be avoided since severe hypotension may re fall in peripheral resistance without a compensatory increase output. If survival is threatened by the arrhythmia, BRETYLOL m but vasoconstrictive catecholamines should be given promptly hypotension occurs.

USE IN PREGNANCY

The safety of BRETYLOL in human pregnancy has not been e However, as the drug is intended for use only in life-threatening si may be used in pregnant women when its benefits outweigh th risk to the fetus.

USE IN CHILDREN

The safety and efficacy of this drug in children has not been BRETYLOL has been administered to a limited number of pediatr but such use has been inadequate to define fully proper dosage tions for use.

PRECAUTIONS

1. Dilution for Intravenous Use: BRETYLOL should be dilute BRETYLOL with four parts of Dextrose Injection, USP or Sodiu Injection, USP) prior to intravenous use. Rapid intravenous ad may cause severe nausea and vomiting. Therefore, the diluted solu be infused over a period greater than 8 minutes. In treating exist ular fibrillation BRETYLOL should be given as rapidly as possib be given without dilution.

2. Use Various Sites for Intramuscular Injection: When tramuscularly, not more than 5 ml should be given in a site, a sites should be varied since repeated intramuscular injection int site may cause atrophy and necrosis of muscle tissue, fibros degeneration and inflammatory changes.

3. Reduce Dosage in Impaired Renal Function: Since BR excreted principally via the kidney, dosage should be reduced with impaired renal function.

ADVERSE REACTIONS

Hypotension and postural hypotension have been the most fr ported adverse reactions (see Warnings section). Nausea and curred in about three percent of patients, primarily when BRE administered rapidly by the intravenous route (see Precautio Vertigo, dizziness, light-headedness and syncope, which someti panied postural hypotension, were reported in about 7 patients

Bradycardia, increased frequency of premature ventricular c transitory hypertension, initial increase in arrhythmias (see Warni precipitation of anginal attacks, and sensation of substernal pr also been reported in a small number of patients, i.e., approx patients in 1000.

Renal dysfunction, diarrhea, abdominal pain, hiccups, erythe ular rash, flushing, hyperthermia, confusion, paranoid psychosi lability, lethargy, generalized tenderness, anxiety, shortness of phoresis, nasal stuffiness and mild conjunctivitis, have been about 1 patient in 1000. The relationship of BRETYLOL adm these reactions has not been clearly established.

DOSAGE AND ADMINISTRATION

BRETYLOL is to be used clinically only for treatment of lif ventricular arrhythmias under constant electrocardiographic moni there is a delay in onset of its antiarrhythmic action, BRETYLOI considered or used as a replacement for rapidly-acting antiarrhy currently in use. The clinical use of BRETYLOL is for short-te Patients should either be kept supine during the course of BR apy or be closely observed for postural hypotension. The optimal ule for parenteral administration of BRETYLOL has not beer There is comparatively little experience with dosages 30 mg/kg/day, although such doses have been used without verse effects. The following schedule is suggested:

A. For Immediately Life-threatening Ventricular Arrhyt Ventricular Fibrillation: Administer undiluted BRETYLOL at 5 mg/kg of body weight by rapid intravenous injection. Other pulmonary resuscitative procedures, including electrical cardiov be employed prior to and following the injection in accordance with practice. If ventricular fibrillation persists, the dosage may be in mg/kg and repeated at 15 to 30 minute intervals until a total dos than 30 mg/kg of body weight has been given. For maintenanc below.

B. Other Ventricular Arrhythmias:

1. Intravenous Use: *BRETYLOL must be diluted as f Intravenous administration:* Using aseptic technique, dilute one BRETYLOL ampul (10 ml containing 500 mg bretylium minimum of 50 ml with Dextrose Injection, USP or Sodium tion, USP.

Administer the diluted solution at a dosage of 5 to 10 mg B kg of body weight by intravenous infusion over a period great utes. More rapid infusion may cause nausea and vomiting. A may be given in 1 to 2 hours if the arrhythmia persists.

2. For Intramuscular Injection: (*Do not dilute BRETYLOL muscular injection.*) Inject 5 to 10 mg BRETYLOL per kg o Dosage may be repeated in 1 to 2 hours if the arrhythmia p after maintain with same dosage every 6 to 8 hours.

Intramuscular injection should not be made directly into o nerve, and the site of injection should be varied on repeated i

C. Maintenance Dosage: The diluted BRETYLOL solution istered by intermittent bolus infusion or by constant infusion

1. Intermittent Infusion: Infuse the diluted solution at a dos mg BRETYLOL per kg body weight, over a period greater th every 6 hours. More rapid infusion may cause nausea and v

2. Constant Infusion: Infuse the diluted solution at a dosag BRETYLOL per minute.

Dosage of BRETYLOL should be reduced and discontinued under electrocardiographic monitoring. Other appro rhythmic agents should be substituted, if indicated.

HOW SUPPLIED

NDC 0094-0012-10: 10 ml ampul containing 500 mg bretyl Water for Injection, USP, pH adjusted, when necessary, wit chloric acid or sodium hydroxide. Sterile, pyrogen-free.

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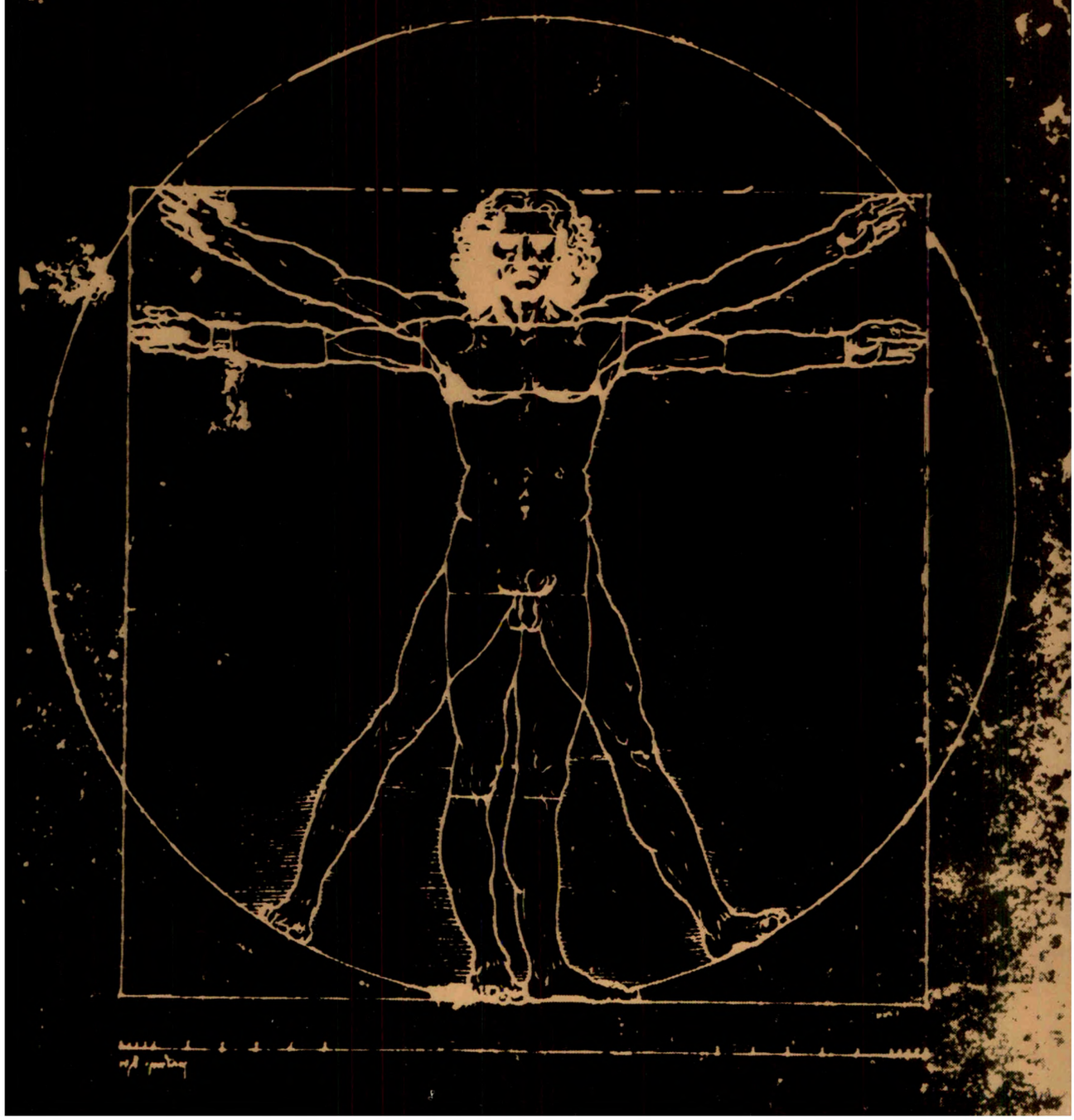
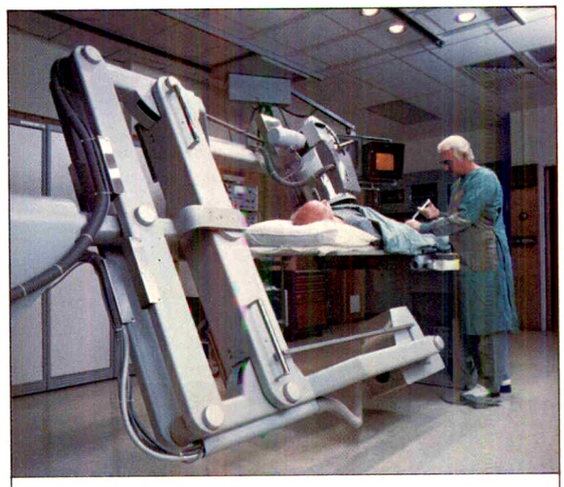


Poly Diagnost C



The parallelogram construction of the Poly Diagnost C permits the patient to remain stationary, leaving the physician more relaxed and able to concentrate fully on the procedure. Insuring maximum safety for both patient and operator, the Poly C provides both routine and cranio-caudal views that insure clear, unobstructed views of overlapping vessels. Stenoses which might have been obscured can be detected with a high degree of efficiency and operational ease.

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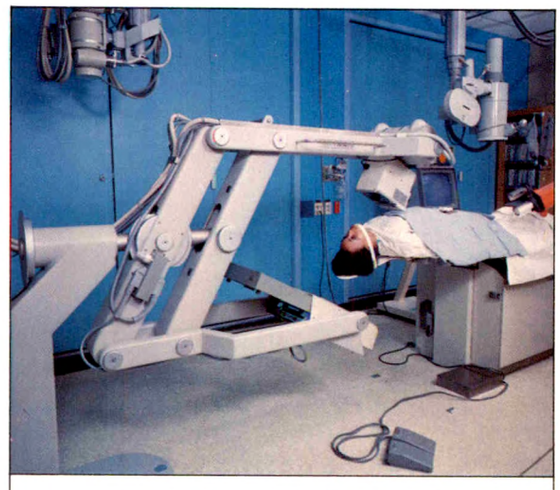
Poly Diagnost N



Designed specifically for cerebral angiography at 2:1 magnification, the Poly Diagnost N easily provides views of the patient previously difficult (or impossible) to achieve. The parallelogram construction allows full rotation around the long axis of the body *and* the maximum desirable head-to-foot angulation. The unique construction insures all motions are isocentric and all results are distortion free.

Designed for use in single or bi-plane operation with a Puck rapid film changer, the Poly N lends itself to extensions for more dedicated requirements, such as the latest configuration with a quickly interchangeable image intensifier and a rapid film changer.

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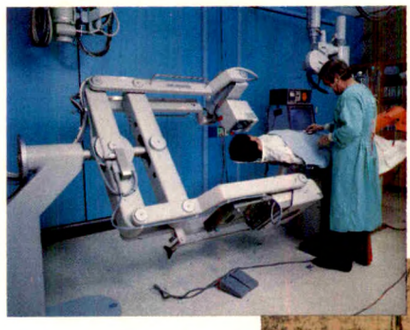
Philips Angiography Systems.



Poly Diagnost N

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Philips' new universal angiography system for the most flexible filming of cerebral, thoracic, abdominal and peripheral angiography, with full provision for occasional cardiovascular examinations.

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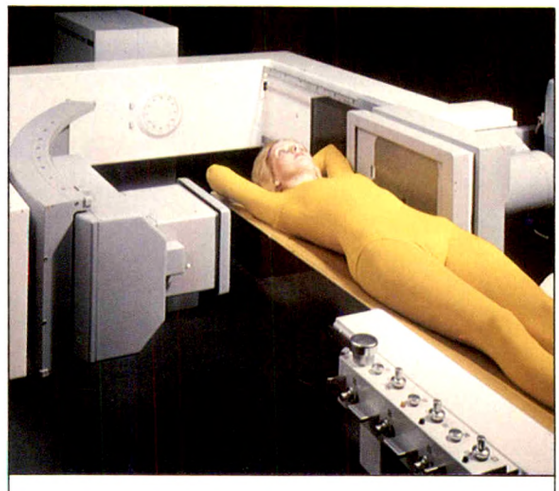
Poly Diagnost UPI



A universal system with revolutionary design, the Poly Diagnost UPI features a rotating U-arm that carries the X-ray tube and an image intensifier and rapid film changer which are quickly interchangeable.

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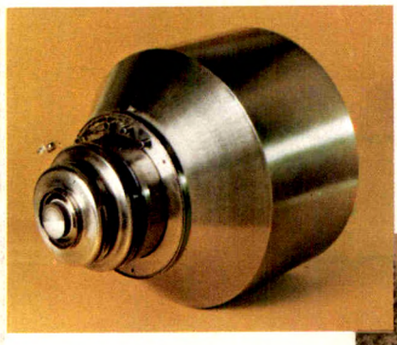

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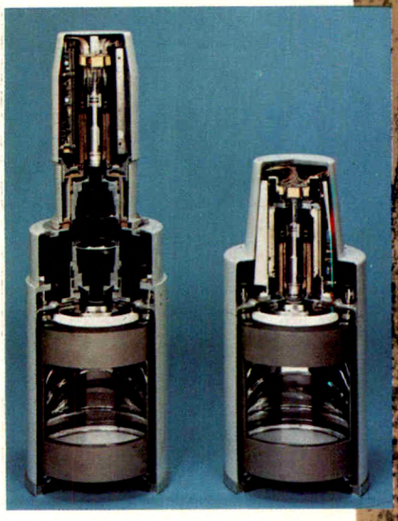

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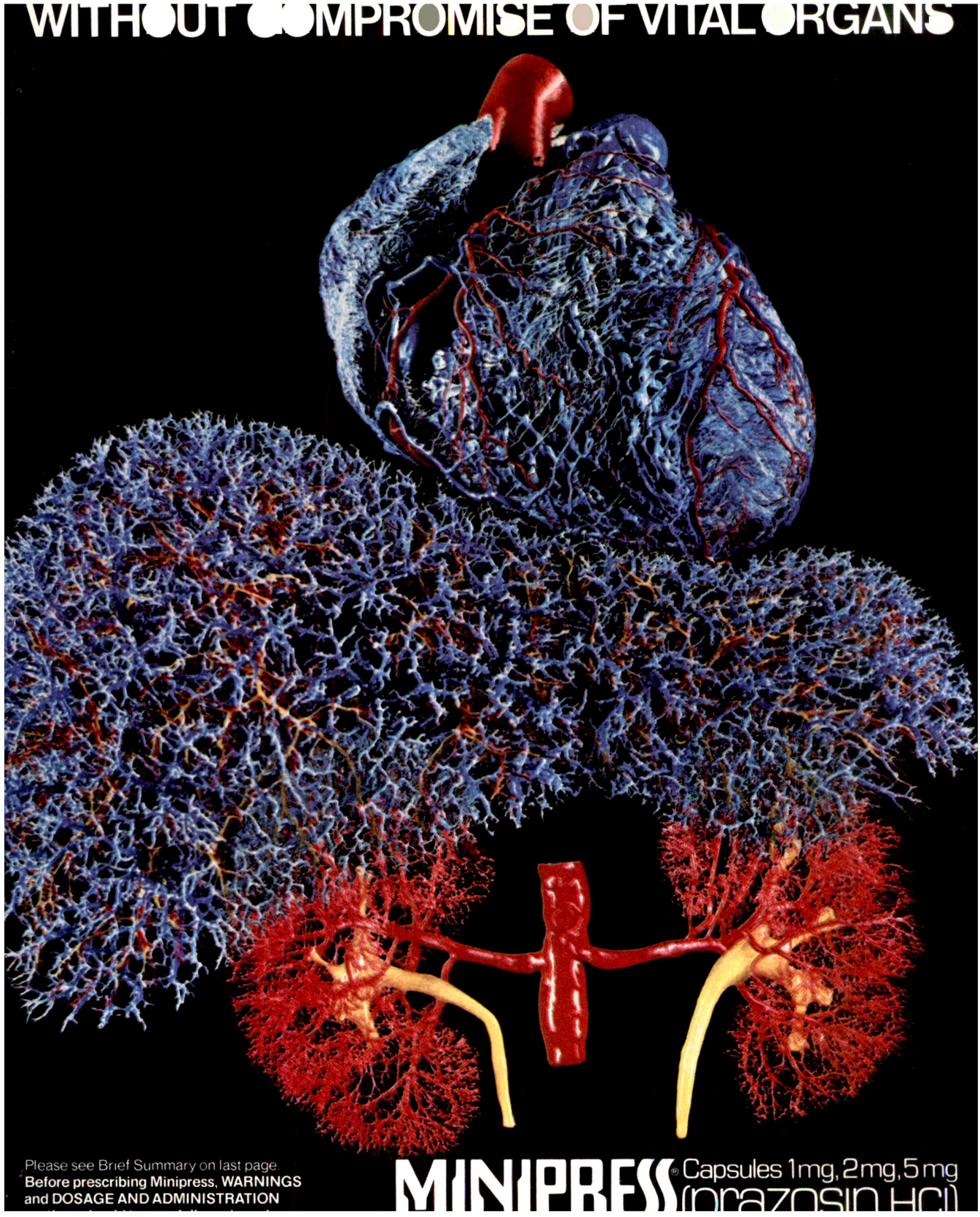
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Please see Brief Summary on last page.
Before prescribing Minipress, WARNINGS
and DOSAGE AND ADMINISTRATION
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(prazosin HCl)

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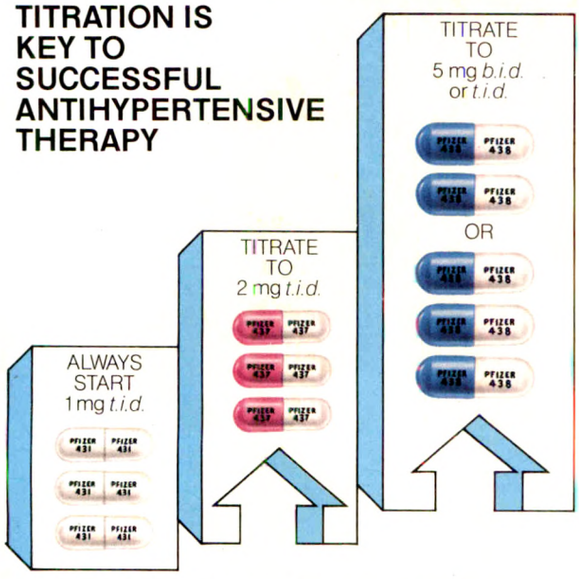
TITRATION IS KEY TO SUCCESSFUL ANTIHYPERTENSIVE THERAPY



USUAL MAXIMUM DAILY DOSAGE: 20 mg given in divided doses (*b.i.d.* or *t.i.d.*). A few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses.

- **Initial therapy:** Whether using Minipress in combination with other agents or alone, the starting dosage is 1 mg *t.i.d.* If response is not adequate by the next visit, the dosage should be increased to 2 mg *t.i.d.*
- **Dosage titration:** Thereafter, titrations of Minipress should be carried out according to patient response. Dosage may be slowly increased to a daily maximum of 20 mg given in divided doses. Although some patients may be controlled on 1 mg *t.i.d.*, generally 6 mg to 15 mg daily will be needed in the majority of responding patients in order to achieve optimal blood pressure control.
- **Maintenance therapy:** After initial titration, patients may be maintained on a *b.i.d.* or *t.i.d.* dosage regimen.
- If optimum control is not achieved in patients receiving Minipress and a diuretic, consider adding another Step 2 antihypertensive agent.
- If optimum control is not achieved with Minipress as the initial agent, consider adding a diuretic.
- When adding a diuretic or other antihypertensive agent, Minipress dosage should be reduced to 1 mg or 2 mg *t.i.d.* and retitrated as needed.
- Available in 1-mg, 2-mg, and 5-mg capsules.

REMOVE PAGE AND FOLD ALONG DOTTED LINE AND SAVE FOR REFERENCE

BRIEF SUMMARY

MINIPRESS® (prazosin hydrochloride) Capsules *For Oral Use*

INDICATIONS. MINIPRESS (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS. MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS. The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION. The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. Higher doses usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED. MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437), and 5 mg (blue and white #438) capsules in bottles of 250, and unit-dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

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Antiarrhythmic Drug Effect Assessed From Ventricular Arrhythmia Reduction in the Ambulatory Electrocardiogram And Treadmill Test: Comparison of Propranolol, Procainamide and Quinidine

ROGER A. WINKLE, MD, FACC
ALAN H. GRADMAN, MD
JOHN W. FITZGERALD, MD
With the technical assistance of
PATRICIA A. BELL

Stanford, California

A 5 week study was performed in 17 patients with frequent ventricular ectopic complexes. The study design comprised an initial control period, 1 week each of treatment with propranolol (240 mg daily), procainamide (3.0 g daily) and quinidine (1.8 g daily) and a final control period. Twenty-four hour ambulatory electrocardiograms and maximal exercise tests were performed each week. For the group, the total number and qualitative types of ventricular ectopic complexes were similar during the two control periods; however, there were large variations among individual patients. Each drug reduced the total number of ventricular ectopic impulses and the percent of patients with each qualitative type. There was agreement between the ambulatory electrocardiogram and treadmill test in three quarters of the drug evaluations. Although it is possible to determine antiarrhythmic drug effects for a group, spontaneous variability in the occurrence of ventricular arrhythmias makes it difficult to evaluate the effects in individual patients.

Several methods for documenting the efficacy of antiarrhythmic measures have been developed. For symptomatic arrhythmias, symptom relief provides a measure of antiarrhythmic efficacy. For asymptomatic arrhythmias, electrocardiographic rhythm strips, treadmill tests or ambulatory electrocardiograms have all been used to determine antiarrhythmic effect. Although there have been many studies evaluating and comparing antiarrhythmic drugs, to date there have been no studies comparing in the same patient the three established drugs that are widely available in this country for suppressing ventricular arrhythmias. There have been few careful comparisons or critical analyses of the ambulatory electrocardiogram and the exercise treadmill test as tools for documenting antiarrhythmic drug effects. In this study we assessed the antiarrhythmic effects of propranolol, procainamide and quinidine, measured as a reduction in both total number and qualitative types of ventricular ectopic complexes in the ambulatory electrocardiogram and exercise treadmill test. These techniques for evaluating antiarrhythmic effects are compared, and the magnitude and clinical implications of spontaneous variations in the occurrence of ventricular ectopy are examined.

Methods

Protocol Design

Seventeen patients, 13 men and 4 women, were studied. Their average age was 53.5 years (range 33 to 67). Nine patients had coronary artery disease, one had mitral valve prolapse and seven had no apparent cardiac disease other than ventricular arrhythmias. Each patient gave written informed consent, and the protocol was approved by the Stanford Medical Committee on the Use of Human Subjects in Research. Patients were referred by their physicians because of

From the Division of Cardiology, Stanford University School of Medicine, Stanford, California.
This study was supported in part by Grant HL-5866 from the National Institutes of Health, Bethesda, Maryland, and by the Mervin Morris Cardiac Research Fund. Dr. Winkle is the recipient of a Mellon Foundation Fellowship. Manuscript received February 21, 1978; revised manuscript received April 11, 1978, accepted April 12, 1978.

Address for reprints: Roger A. Winkle, MD, Cardiology Division, Stanford University School of Medicine, Stanford, California 94305.

TABLE I

Total Number of Premature Ventricular Complexes

Case no.	Control Period 1	Propranolol	Procainamide	Quinidine	Control Period 2
	A. In 24 Hour Ambulatory Electrocardiogram				
1	854	202	144	—	1171
2	28,416	13,344	9888	2	3552
3	12,000	12,480	—	163	14,976
4	10,656	5856	8544	—	18,144
5	*	*	—	*	*
6	26,112	29,376	—	4493	40,512
7	4128	192	269	0	7008
8	2784	106	14	11	1027
9	7680	7392	15,552	20,832	7488
10	3840	1373	566	893	7968
11	2544	739	29	22	1949
12	1728	739	96	7	278
13	2496	1507	106	1	221
14	2016	48	—	3456	1085
15	4800	816	—	—	14,304
16	1613	230	—	989	403
17	13,632	12,672	—	18	7584
	B. In Treadmill Exercise Test				
1	79	14	0	—	45
2	61	5	10	0	73
3	127	304	—	0	188
4	†	†	†	—	†
5‡	0	35	—	0	3
6	803	295	—	156	803
7‡	0	0	0	0	0
8	22	4	1	1	32
9	166	170	215	87	185
10	60	1	5	30	3
11	12	10	1	0	1
12‡	2	0	0	0	0
13	34	0	0	0	15
14	28	0	—	13	0
15	162	3	—	—	161
16	39	20	—	31	12
17	99	144	—	1	46

* Accurate quantitation of premature ventricular complexes not possible because of parasystole.

† Patient unable to exercise consistently because of lung disease.

‡ Patients 5, 7 and 12 were considered to have too few premature ventricular complexes during control period 1 of the treadmill exercise test and were not included in the quantitative analysis of the data.

known ventricular ectopic activity. For each patient, antiarrhythmic therapy was considered optional in that the known arrhythmias were not an immediate threat to life. Patients with known allergies or intolerance to propranolol, procainamide or quinidine, poorly controlled congestive heart failure, myocardial infarction within the preceding 2 months, advanced degrees of heart block or obstructive pulmonary disease were excluded.

The first week of the 5 week protocol was an initial control period (control period 1). Each patient had at least 10 premature ventricular complexes during exercise and 5 minutes of recovery, or an average of 1 premature ventricular impulse/min over 24 hours during this control period. Propranolol was administered during week 2 in doses of 40 mg every 4 hours (240 mg daily), procainamide during week 3 in doses of 375 mg every 3 hours (3.0 g daily) and quinidine during week 4 in doses of 300 mg every 4 hours (1.8 g daily). Week 5 was a final control period (control period 2). On the final day of each week, a maximal exercise treadmill test following the Bruce protocol[1] and a 24 hour ambulatory electrocardiogram were obtained. Patients were permitted to take drugs at any time during the day as long as they followed the schedule described. Each patient was instructed regarding the importance of dosing intervals and of taking the drug. Patients were given telephone numbers to call in order to report any side effects. The treadmill tests were generally performed at 8:30 AM, and the ambulatory electrocardiograms started immediately after the treadmill tests. For each patient, tests were performed on the same day of the week and the patients were instructed to go about their usual activities.

Antiarrhythmic drug side effects were tabulated as follows: no side effects, side effects present but patient able to continue taking the drug, severe side effects and patient unable to continue taking the drug.

Data Analysis

The frequency of premature ventricular complexes in the ambulatory electrocardiograms was determined using a digital computer system.[2] Five recordings, all made in patients receiving antiarrhythmic therapy, had very infrequent ventricular ectopic complexes, and for these tapes an exact count was obtained. The remaining tapes were analyzed using algorithms that determine the number of premature ventricular complexes in each minute in the recording. To verify accuracy, exact manual counts from representative minutes of electrocardiographic signal were made throughout the recording and compared with the computer count. The average ventricular ectopic complex overcount by the computer was 2.9 ± 3.5 percent (range 0.0 to 15.0) and the undercount was 3.5 ± 3.2 percent (range 0.0 to 16.2). Each tape was also analyzed for the occurrence of multifocal or paired premature ventricular complexes, bigeminy and ventricular tachycardia. Arrhythmia frequency in the ambulatory electrocardiogram was expressed as premature ventricular complexes/15 minutes averaged over the 24 hour period, and as the total number in 24 hours (Table IA). From these data, the percent change in ventricular ectopic complex frequency from control period 1 to control period 2 was determined. For each drug, the quantitative antiarrhythmic effect was assessed as the percent change in frequency of premature ventricular complexes in the ambulatory electrocardiogram recorded while the patient was taking that drug from the average frequencies recorded during the two control periods.

For each exercise treadmill test, the total number of premature ventricular complexes (Table IB) and the occurrence of multifocal or paired premature ventricular complexes, bigeminy or ventricular tachycardia were determined by continuous recording during exercise and 5 minutes of recovery. From these data, the percent change in total number of premature ventricular complexes from control period 1 to control period 2 was determined. The quantitative antiarrhythmic effect for each drug was determined by comparing the total number of ventricular ectopic impulses during drug therapy with the average number of such impulses during the two control periods. The total number of minutes of exercise and maximal heart rates for the two control tests and for each drug was compared with the average values of the two control tests.

Statistical Analysis

Two separate statistical methods were used to analyze much of the data. Statistical comparison of the premature ventricular complex frequency for the two control ambulatory electrocardiograms was performed by a matched pair t test comparison of log (NC1 + 1.01) and log (NC2 + 1.01) where NC1 = the total number of premature ventricular impulses in 24 hours during the initial control recording and NC2 = the total number of premature ventricular impulses in 24 hours during the final control recording. The second method used

was the Wilcoxon rank sum test comparing NC1 and NC2. For each of the three drugs a matched pair t test was performed comparing log (ND + 1.01) and [log (NC1 + 1.01) + log (NC2 + 1.01)]/2, where ND = the total number of premature ventricular impulses in 24 hours during the drug recording. The Wilcoxon rank sum test comparing ND with (NC1 + NC2)/2 was also used. Similar log transformations, matched t test comparisons and rank sum tests were made for the total number of premature ventricular impulses occurring in the exercise tests. Throughout this report, whenever two P values are given, the first was obtained by applying the t test to the transformed data and the second by using the rank sum test. For the comparison of the number of minutes of exercise and the maximal heart rates on the treadmill test, a matched pair t test was performed using nontransformed data. All P values are for two-tailed comparisons.

Results

Comparison of Control Periods 1 and 2

Ambulatory electrocardiograms: Quantitative data on premature ventricular complexes were available from the ambulatory electrocardiographic tapes for 16 of the 17 patients in this study. The tapes of one patient with parasystole could not be quantitated accurately because of the large numbers of fusion beats that at times were difficult to distinguish from sinus beats. The average ventricular ectopic impulse frequency in the ambulatory electrocardiographic recordings for these 16 patients during the initial control recording (control period 1) and the final control recording (control period 2) performed 4 weeks later were 81.5 ± 89.0 and 83.1 ± 108 premature ventricular complexes per 15 minutes per patient, respectively. The total number of premature ventricular complexes ranged from 854 to 28,416 for control period 1 and from 221 to 40,512 for control period 2. For the group, the total number of premature ventricular complexes in the two control ambulatory electrocardiograms were statistically similar. However, data from individual patients demonstrated marked spontaneous fluctuation between the two recording periods (Fig. 1). Although the median percent change in premature ventricular complex frequency over the 4 week period was only −12 percent (control period 2 compared with control period 1), values in individual patients ranged from −91 percent to +198 percent. Five of the 16 patients (31 percent) showed a spontaneous decline of more than 50 percent in frequency of premature ventricular complexes; only 1 patient (6 percent) had a spontaneous reduction of more than 90 percent.

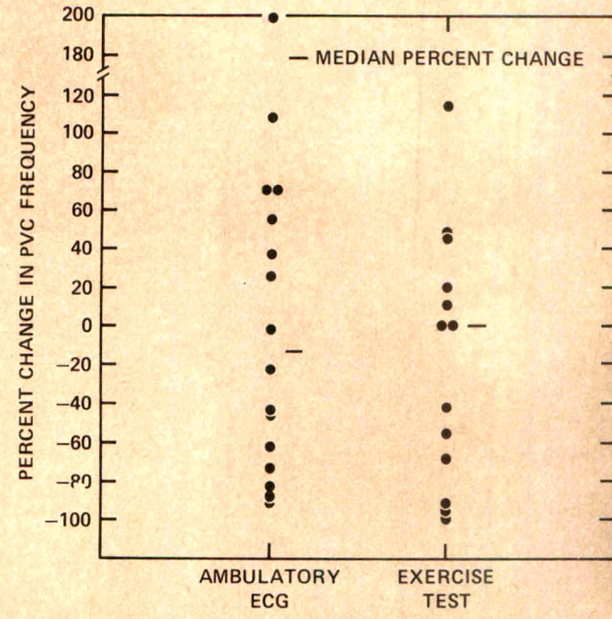

FIGURE 1. Spontaneous change in the occurrence of premature ventricular complexes (PVC) for the two 1 week control periods. Shown are the percent changes in the number of premature ventricular complexes in control test 2 compared with the number in control test 1 for the ambulatory electrocardiogram (ECG) (**left**) and treadmill exercise test (**right**). The wide range of individual patient variations is apparent; however, for the group, the median percent changes for the two tests were only −12 percent and 0 percent, respectively.

That the average frequencies for the group were similar for the two control recordings reflects the occurrence of these spontaneous changes in both directions, with seven patients demonstrating an increase and nine patients a decrease in premature ventricular complex frequency (Fig. 1).

The occurrence of multifocal or paired premature ventricular impulses, bigeminy and ventricular tachycardia in the two control ambulatory electrocardiograms was compared in all 17 patients. The total number of patients exhibiting pairs, bigeminy and ventricular tachycardia was similar for each of the two recordings (Table II). Multifocal premature ventricular complexes showed a slight difference for the two recordings, occurring in 11 patients in control recording 1 and in 7 in control recording 2. Although the *total*

TABLE II

Ambulatory Electrocardiogram: Number of Patients With Each Type of Ventricular Ectopic Activity

	Control Period 1 (17 patients)	Propranolol (17 patients)	Procainamide (10 patients)	Quinidine (14 patients)	Control Period 2 (17 patients)
Multifocal	11 (65%)	7 (41%)	4 (40%)	2 (14%)	7 (41%)
Pairs	9 (53%)	5 (29%)	4 (40%)	3 (21%)	7 (41%)
Bigeminy	13 (77%)	10 (59%)	4 (40%)	4 (29%)	12 (71%)
Ventricular tachycardia	3 (18%)	1 (6%)	1 (10%)	1 (7%)	2 (12%)

TABLE III

Reproducibility of Each Type of Complex Ventricular Arrhythmia for the Two Control Periods (C1 and C2)

	Number of Patients With Arrhythmia		
	Both C1 and C2	Only C1 or C2	Total
Ambulatory electrocardiogram			
Multifocal	7	4	11
Pairs	5	6	11
Bigeminy	11	4	15
Ventricular tachycardia	0	5	5
Treadmill test			
Multifocal	1	9	10
Pairs	4	3	7
Bigeminy	3	5	8
Ventricular tachycardia	1	0	1

number of patients with each type of complex arrhythmia was similar for the two control recordings, individual patients often demonstrated a given type of arrhythmia in only one of the two recordings. Table III summarizes the reproducibility of each type of complex ventricular arrhythmia for the two recordings. Although the numbers are small for each type, it was common for these complex arrhythmias to be recorded in only one of the two control periods. This spontaneous variability was most apparent for pairs and ventricular tachycardia. In fact, not one of the five patients with ventricular tachycardia had this rhythm recorded in *both* control ambulatory electrocardiograms.

Exercise treadmill tests: Quantitative data on premature ventricular complexes were available for 13 of the 17 patients. One patient was unable to exercise consistently because of severe dyspnea related to restrictive pulmonary disease, and three patients had too few ventricular ectopic complexes (less than 10) in the control treadmill tests to permit adequate quantitative comparison of the two control tests. For the remaining 13 patients, the average number of premature ventricular complexes was 130 ± 208 and 120 ± 217 per patient per test in control period 1 and control period 2, respectively, with the median percent change being 0. Statistical analysis revealed no difference for the two control exercise tests. As with the ambulatory electrocardiograms, individual patients demonstrated marked spontaneous change in total number of premature ventricular complexes from control period 1 to control period 2 (percent change ranging from −100 percent to +115 percent) (Fig. 1). Three of the 13 patients (23 percent) demonstrated greater than 90 percent reduction in the number of premature ventricular complexes from the first to the second control recordings. Five patients demonstrated an increase and eight a decrease in the number of premature ventricular complexes between the two recordings.

The occurrence of multifocal or paired premature ventricular complexes, bigeminy and ventricular tachycardia in the two control exercise treadmill tests was compared. The total number of patients exhibiting pairs, bigeminy and ventricular tachycardia was similar for each of the two exercise tests (Table IV). As with the ambulatory electrocardiogram, multifocal premature ventricular complexes showed a difference for the two exercise tests, with nine patients having multifocal premature ventricular complexes in control period 1 and only two in control period 2. There was a poor reproducibility of complex types of arrhythmias for the two control exercise tests (Table III).

The number of minutes of exercise (7.1 ± 3.0 versus 7.8 ± 2.8 minutes) *and maximal heart rate* (143 ± 19 versus 140 ± 18 beats/min) was not significantly different for the two control tests. In contrast to the total number and qualitative types of premature ventricular complexes recorded in the exercise treadmill tests, there were no large individual variations in the number of minutes of exercise and maximal heart rate achieved in the two control exercise tests.

The spontaneous variability in arrhythmia in both the ambulatory electrocardiograms and treadmill tests was similar for patients with and without coronary artery disease.

Propranolol

Side effects: All patients completed the 1 week course of propranolol, although one patient spontaneously reduced his dose to 40 mg every 6 hours. Ten patients experienced no side effects with propranolol and seven had minor side effects. Five patients noted mild fatigue. Other side effects included depression, impotence and mild gastrointestinal complaints. Propranolol had the least severe side effects among the three drugs studied.

Ambulatory electrocardiograms: There was a reduction in ventricular ectopic frequency in the ambu-

TABLE IV

Exercise Treadmill Test: Number of Patients With Each Type of Ventricular Ectopic Activity

	Control Period 1 (16 patients)	Propranolol (16 patients)	Procainamide (9 patients)	Quinidine (14 patients)	Control Period 2 (16 patients)
Multifocal	9 (56%)	3 (19%)	0 (0%)	0 (0%)	2 (12%)
Pairs	6 (38%)	2 (12%)	1 (11%)	1 (7%)	5 (31%)
Bigeminy	6 (38%)	6 (38%)	2 (22%)	2 (14%)	5 (31%)
Ventricular tachycardia	1 (6%)	0 (0%)	0 (0%)	0 (0%)	1 (6%)

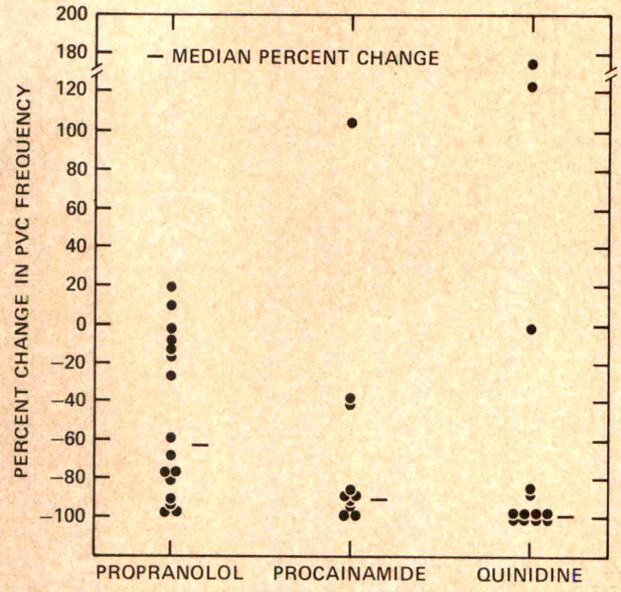

FIGURE 2. Percent change in premature ventricular complex (PVC) frequency in the 24 hour ambulatory electrocardiogram for each of the three drugs compared with the average number in control periods 1 and 2. Although each drug was associated with a marked reduction in ectopic complexes, quinidine was most often associated with almost 100 percent reduction.

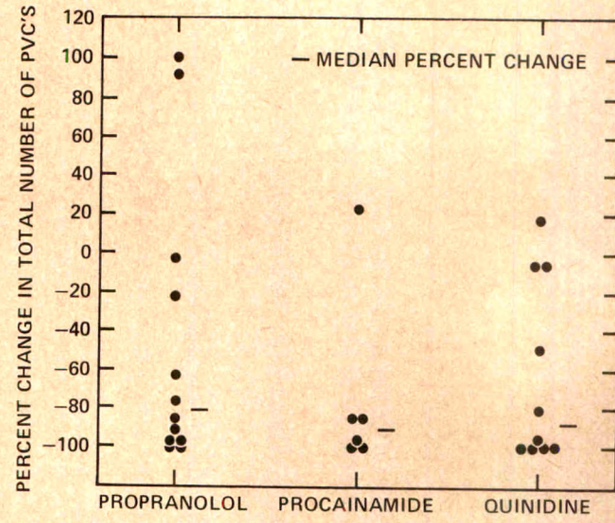

FIGURE 3. Percent change in the total number of premature ventricular complexes (PVC's) in the exercise treadmill test for each of the three drugs compared with the average number in control periods 1 and 2. Each drug was associated with a marked reduction in ectopic complexes.

latory electrocardiogram recorded during treatment with propranolol compared with the control recordings in 14 of the 16 patients with quantitated data. Ventricular ectopic complex suppression was 90 percent or greater in only four of these patients (25 percent). The median percent reduction for all 16 patients was −63 percent (range −97 to +20 percent) (Fig. 2). The reduction in the total number of premature ventricular complexes was statistically significant ($P < 0.01$, $P < 0.052$), and there was also a reduction in the number of patients with all types of complex ventricular ectopy (Table II).

Exercise treadmill tests: The median reduction in number of premature ventricular beats occurring during the exercise test while the patient was receiving propranolol therapy was −81 percent (range −100 to +100 percent) (Fig. 3). The reduction in the total number of premature ventricular complexes was statistically significant ($P < 0.01$, $P < 0.08$) and there was also a reduction in the number of patients experiencing each type of complex ventricular form except bigeminy (Table IV). The duration of exercise (7.1 ± 3.0 minutes) was similar to the control level. The maximal heart rate (103.7 ± 13.3 beats/min) was reduced from the control value ($P < 0.001$).

Procainamide

Side effects: Seven of the 17 patients were unable to complete the week of treatment with procainamide, and 2 others experienced minor side effects. This drug had the most severe side effects among the three drugs. These included a variety of gastrointestinal complaints, malaise, fever, rash, visual disturbances, diaphoresis, arthralgia, insomnia and myalgias.

Ambulatory electrocardiograms: There was a reduction in premature ventricular complex frequency in the ambulatory electrocardiogram recorded during treatment with procainamide compared with the control recordings in 9 of 10 patients. This reduction exceeded 90 percent in 6 of the 10 (60 percent). The median percent reduction for all 10 patients was −90 percent (range −99 to +105 percent) (Fig. 1). The reduction in the total number of premature ventricular complexes was statistically significant ($P < 0.01$, $P < 0.052$), and there was a reduction in the number of patients with all types of complex ventricular ectopy (Table II).

Exercise treadmill tests: The median reduction in number of premature ventricular complexes during the exercise treadmill test performed during procainamide therapy was −90 percent (range −100 to +22 percent) (Fig. 3). The reduction in the total number of premature ventricular complexes was statistically significant ($P < 0.025$, $P < 0.064$), and there was also a reduction in the number of patients experiencing each type of complex ventricular beat (Table IV). Neither the duration of exercise (7.6 ± 2.1 minutes) nor the maximal heart rate (144.0 ± 14.8 beats/min) differed from the control level.

Quinidine

Side effects: Three of the 17 patients were unable to complete the week of treatment with quinidine, and 8 experienced side effects. Side effects included gastrointestinal complaints, fever, cinchonism, fatigue, insomnia and syncope.

Ambulatory electrocardiograms: Premature ventricular complex frequency was decreased in the

TABLE V

Percent Suppression of Premature Ventricular Complexes in the Ambulatory Electrocardiogram Induced by Each Antiarrhythmic Drug in the Eight Patients Completing 1 Week of Treatment With All Three Drugs

Case no.	Propranolol	Procainamide	Quinidine
2	−16	−38	−100
7	−97	−95	−100
8	−94	−99	−99
9	−2.5	+105	+175
10	−77	−90	−85
11	−67	−99	−99
12	−26	−90	−99
13	+10.5	−92	−100

ambulatory electrocardiogram recorded during quinidine therapy compared with control recordings in 11 of 13 patients. This reduction exceeded 90 percent in 8 of the 13 patients (62 percent). The median percent reduction was −99 percent (range −100 to +175 percent) (Fig. 2). The reduction in the total number of premature ventricular complexes was statistically significant ($P < 0.005$, $P < 0.0026$). Quinidine caused the largest reduction in complex ventricular forms (Table II).

Exercise treadmill tests: The median reduction in number of premature ventricular beats occurring during the exercise treadmill test performed during quinidine therapy was −88 percent (range −100 to +19 percent) (Fig. 3). The reduction in total number of premature ventricular complexes was statistically significant ($P < 0.025$, $P < 0.036$). There was also a reduction in the number of patients with each type of complex arrhythmia (Table IV). Neither the duration of exercise (7.8 ± 2.6 minutes) nor maximal heart rate (141.8 ± 14.9 beats/min) differed from the control level.

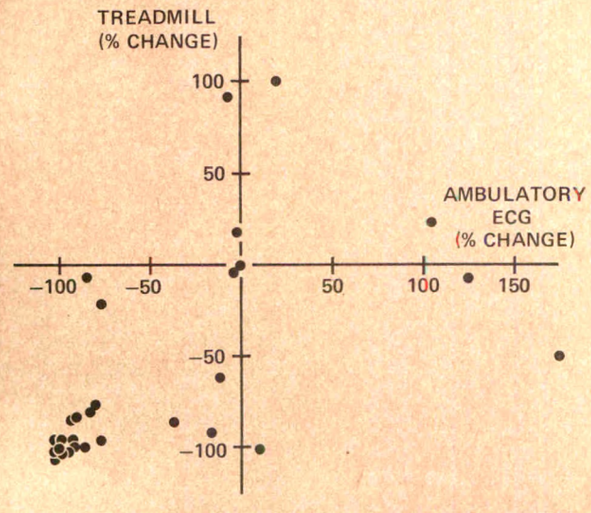

FIGURE 4. Comparison of the ambulatory electrocardiogram (ECG) and exercise treadmill test in evaluating antiarrhythmic response. The **horizontal axis** gives the percent change in premature ventricular complex frequency compared with the average of the two control periods as measured with the ambulatory electrocardiograms; the **vertical axis** gives these data for the exercise test. Although many drug trials showed premature ventricular complex suppression in both tests, sometimes the two tests gave disparate results.

Comparison of the Three Drugs in the Same Patient

Eight patients completed the 1 week trial with all three drugs. There was generally good agreement between the quantitative antiarrhythmic response to procainamide and quinidine; however, the antiarrhythmic response to propranolol often differed from the response to the other two agents (Table V).

Overall drug efficacy: Overall, 11 of the 16 patients had 90 percent suppression of premature ventricular complexes in the ambulatory electrocardiogram during treatment with at least one of the three drugs. However, 4 of these 11 noted minor side effects from the drug. Thus, only 7 of 16 patients (44 percent) could have had 90 percent suppression without side effect using these three drugs. The patterns of response to each of these three drugs could not be related to the underlying cardiac diagnosis.

Comparison of ambulatory electrocardiogram and exercise treadmill test: Quantitative ventricular ectopic beat data were available for both the ambulatory electrocardiogram and the exercise treadmill test for 28 of the 1 week drug trials. The directional change (increase or decrease) in ventricular ectopic complex frequency was the same in 23 of these 28 tests (82 percent) (Fig. 4). In 20 of these 28 drug trials either an exercise test or an ambulatory electrocardiogram demonstrated more than 70 percent reduction in ectopic beat frequency. Of these, 15 (75 percent) showed greater than 70 percent reduction in both tests. In 13 of the drug trials either an ambulatory electrocardiogram or an exercise test demonstrated greater than 90 percent reduction in ectopic beat frequency. Of these, 9 (69 percent) showed greater than 90 percent reduction in both tests. Thus, in approximately three quarters of the instances there was reasonable agreement between the quantitative antiarrhythmic responses assessed with these two techniques; however, in the remaining instances there were often large discrepancies (Fig. 4).

For 72 of the 1 week control and drug therapy periods, both an ambulatory electrocardiogram and an exercise

TABLE VI

Comparison of Ambulatory Electrocardiogram and Treadmill Exercise Test in Detecting Complex Ventricular Arrhythmias

Arrhythmia	Treadmill and Ambulatory ECG	Treadmill Only	Ambulatory ECG Only	Total
Multifocal	8 (22%)	6 (17%)	22 (61%)	36
Pairs	11 (38%)	4 (14%)	14 (48%)	29
Bigeminy	19 (45%)	2 (5%)	21 (50%)	42
Ventricular tachycardia	1 (12%)	1 (12%)	6 (75%)	8
Totals	39 (34%)	13 (11%)	63 (55%)	115

ECG = electrocardiogram.

treadmill test were available to compare these two tests for detecting each type of complex ventricular arrhythmia (Table VI). Complex ventricular arrhythmias were most commonly (55 percent of cases) detected only in the ambulatory electrocardiogram; in 34 percent they were detected in both tests and infrequently (11 percent of cases) they were detected in the exercise treadmill test alone.

Discussion

Determining the effectiveness of antiarrhythmic therapy for ventricular arrhythmias can be a difficult problem. For some patients elimination of serious symptoms provides a reasonable end point for therapy.[3] Judging the success of therapy for asymptomatic arrhythmias is a more complex problem. Proof that treating such arrhythmias prevents future disability can be determined only in large scale intervention trials.[4,5] For individual patients, physicians often rely on other methods to document the effectiveness of antiarrhythmic drugs. Two goals of our study were to compare the ambulatory electrocardiogram and exercise treadmill test and to evaluate critically the use of qualitative and quantitative ventricular arrhythmia reduction for determining antiarrhythmic effect.

Spontaneous variability in ventricular ectopy: One important finding of our study was the marked spontaneous variability in ventricular ectopy for individual patients when the two control periods were compared. Whether for each patient this was a 4 week trend or merely day to day fluctuation cannot be determined from our data. We could not account for these fluctuations on the basis of any apparent occupational, physical or emotional changes. The changes in frequency of ventricular ectopy were in both directions, and the average frequency for the group as a whole was statistically similar for both control periods. Each drug induced a significant group reduction in ventricular ectopy. The difficult problem is to determine when an *individual patient* has responded to an antiarrhythmic drug or when an observed reduction in ventricular ectopy is due to a spontaneous decrease.

In this study a 90 percent spontaneous reduction in the frequency of premature ventricular complexes was unusual in the ambulatory electrocardiogram, occurring in only 1 of 16 patients (6 percent), whereas 90 percent or greater reduction was frequently achieved while a patient was taking antiarrhythmic drugs, especially procainamide and quinidine. Although some investigators[6] have utilized a criterion of only 25 percent reduction and we have generally used 70 to 75 percent reduction, perhaps a criterion of 90 percent reduction of premature ventricular complexes should be required when studying an individual patient to be certain that one is measuring a drug effect. Such a stringent criterion will decrease the number of false positive apparent drug responses resulting from a spontaneous decrease in premature ventricular complexes, but it will undoubtedly exclude some true drug responses. This may be especially true for drugs such as propranolol, which infrequently resulted in a 90 percent reduction in ectopic frequency in individual patients yet demonstrated considerable antiarrhythmic effect for the group as a whole. Our data also indicate that spontaneous increases in the frequency of premature ventricular complexes are common and do not necessarily represent a drug-induced worsening of ventricular irritability.

Problems in qualitative grading of ventricular arrhythmia: The use of a qualitative arrhythmia grading system for evaluating antiarrhythmic drug effect has several problems. For some patients the occurrence of each qualitative type of ventricular arrhythmia is variable from one ambulatory electrocardiogram or exercise treadmill test to the next, and the disappearance of pairs or ventricular tachycardia between tests may represent spontaneous variation rather than drug effect. Considering an arrhythmia only as present or absent makes no allowance for the number of times a given type of ventricular ectopic activity occurs. Thus, even if an antiarrhythmic drug reduces the number of episodes of ventricular tachycardia from 100 to 1, the patient would be still considered in the same qualitative class. Numerical "grading" of these types of arrhythmias[7] is somewhat arbitrary because little is known about the prognostic importance of each type of ectopic activity and it is unclear whether the various ventricular arrhythmias occur independently or whether they occur as a function of each other or of total ventricular ectopic complex frequency.

Although there may be difficulties in determining when an individual patient responds to an antiarrhythmic drug, group response is easily determined from a statistical comparison of drug and control tests. Evaluation of our data suggested several things of note for statistical analysis. For many individual patients, the occurrence of premature ventricular complexes over 24 hours does not follow either a normal or a Poisson distribution. For a group of patients, the number of premature ventricular complexes may range from only a few to tens of thousands per day, suggesting that some form of transformation should be applied before statistical analysis. Because the log transformation we used did not fully normalize the data, we therefore also analyzed the data using nonparametric statistical methods, which make no assumptions about distribution.

Ambulatory electrocardiogram versus exercise treadmill test: In this study the ambulatory electrocardiogram detected more qualitative types of ventricular arrhythmias than the exercise treadmill test. This increased sensitivity of the ambulatory electrocardiogram for detecting complex ventricular forms has been reported previously for patients with coronary artery disease[8] and mitral valve prolapse.[9] Although there was general agreement between the two tests in determining the antiarrhythmic response of the group as a whole, for individual patients the two tests occasionally gave quite disparate results.

Comparison of propranolol, procainamide and quinidine: This study suggests that of the three drugs tested, propranolol is associated with fewest side effects and procainamide with the most during short-term administration. It is possible that the occurrence of side

effects could have been reduced and the degree of efficacy improved through the use of drug plasma concentration and adjustment of drug dose. However, for logistic reasons, midweek dose adjustments were not carried out in this study.

Both quinidine and procainamide were more likely than propranolol to result in nearly complete arrhythmia suppression. For individual patients, the use of a drug that frequently results in greater than 90 percent reduction in ventricular ectopy may make evaluation of drug response more certain. Overall, on the basis of both side effects and efficacy, our data suggest that quinidine may be the most useful of the three antiarrhythmic drugs for suppressing asymptomatic ventricular ectopy in individual patients. This does not necessarily mean that it is superior for group intervention studies or that it will prove superior for prevention of sudden death. The finding that only 7 of 16 (44 percent) could have had 90 percent ventricular ectopic beat suppression without side effects, using these three drugs, is similar to that of Jelinek et al.[7] in a study that used only procainamide and quinidine.

Implications: Careful documentation of suppression of asymptomatic ventricular ectopic activity is of value for screening and testing new and existing antiarrhythmic drugs. The procedure is time-consuming, even when computer techniques are used. If computer techniques are employed, ectopic impulse counts must be verified in some way for each patient individually because there may be an occasional patient whose tapes cannot be accurately quantitated. The use of sequential ambulatory electrocardiograms or exercise treadmill tests is expensive. The series of ambulatory electrocardiograms and exercise treadmill tests used to evaluate the antiarrhythmic drugs in this study would have cost the patient well over $1,000. At present, this seems excessive for the routine clinical management of patients, in view of the lack of proved benefit of suppressing asymptomatic arrhythmias.

Further work on the spontaneous variability of the types and quantity of ventricular ectopy will be required to determine the most appropriate method for determining individual antiarrhythmic response. Ultimately, it will be necessary to demonstrate what level and what type of arrhythmia suppression, if any, correlate with a reduction in sudden death.

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References

1. **Doan AE, Peterson DR, Blackmon JR, et al:** Myocardial ischemia after maximal exercise in healthy men. A method for detecting potential coronary heart disease? Am Heart J 69:11–21, 1965
2. **Fitzgerald JM, Clappier RR, Harrison DC:** Small computer processing of ambulatory electrocardiograms. In, IEEE Proceedings, Bethesda, 1974, p 31–36
3. **Winkle RA, Alderman EL, Fitzgerald JW, et al:** Treatment of recurrent symptomatic ventricular tachycardia. Ann Intern Med 85:1–7, 1976
4. **Wilhelmsson C, Vedin JA, Wilhelmsen L, et al:** Reduction of sudden deaths after myocardial infarction by treatment with alprenolol. Lancet 2:1157–1159, 1974
5. A Multicentre International Study: Improvement in prognosis of myocardial infarction by long-term beta adrenoreceptor blockade using proctolol. Br Med J 3:735–740, 1975
6. **Cofsky RD, Kennedy HL:** Propranolol and quinidine therapy for chronic ventricular ectopy (abstr). Clin Res 24:612A, 1976
7. **Jelinek MV, Lohrbauer L, Lown B:** Antiarrhythmic drug therapy for sporadic ventricular ectopic arrhythmias. Circulation 49:659–665, 1974
8. **Crawford M, O'Rourke RA, Ramakrishna N, et al:** Comparative effectiveness of exercise testing and continuous monitoring for detecting arrhythmias in patients with previous myocardial infarction. Circulation 50:301–305, 1974
9. **Winkle RA, Lopes MG, Fitzgerald MD, et al:** Arrhythmias in patients with mitral valve prolapse. Circulation 52:73–81, 1975

Reduced Quinidine Clearance in Elderly Persons

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The influence of age on quinidine pharmacokinetics was assessed in 22 healthy male and female volunteers; 14 of the subjects were young (aged 23 to 34 years) and 8 elderly (aged 60 to 69 years). All subjects received 180 to 300 mg of quinidine base by constant rate intravenous infusion over 10 to 15 minutes. The concentration of total and unbound quinidine in multiple serum samples and in urine collected within 48 hours after the administration of quinidine was determined with spectrophotofluorometric assay. Mean kinetic values for total quinidine in the young subjects were: elimination half-life ($t_{1/2\beta}$), 7.3 hours; total volume of distribution (V_d), 2.39 liters/kg; total clearance, 4.04 ml/min per kg; renal clearance, 1.43 ml/min per kg; and percent unbound, 24.6. In the elderly subjects, the values for V_d (2.18 liters/kg) and percent unbound (28.2) did not differ significantly from these values in the young subjects. However, in the elderly subjects $t_{1/2\beta}$ was significantly longer (9.7 hours, $P < 0.05$) and total quinidine clearance significantly less (2.64 ml/min per kg, $P < 0.005$) than in the young subjects. Renal clearance of quinidine in the elderly was also significantly less (0.99 ml/min per kg, $P < 0.05$) than in the young and was associated with lower rates of creatinine clearance in the elderly ($r = 0.66$). Reduced clearance of quinidine and prolongation of its elimination half-life could predispose to toxicity in the elderly unless the dose were appropriately adjusted.

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Elderly persons appear to be more sensitive than young persons to a variety of drugs.[1,2] Age-related changes in renal or hepatic clearance of many drugs[3–6] may lead to excessive drug accumulation and may partly explain the predisposition to adverse drug reactions in the elderly. Quinidine derivatives are commonly administered to elderly persons with cardiac disease, although the influence of age on the pharmacokinetics and clinical effects of quinidine is largely unknown. We studied the disposition of quinidine in a series of young and elderly volunteer subjects.

Methods

Subjects: Twenty-two healthy male and female volunteers participated in this study after giving informed consent (Table I). Fourteen subjects were "young," aged 23 to 34 years, and 8 were "elderly," aged 60 to 69 years. All of the patients had normal laboratory screening profiles. Five of the eight elderly and all of the young subjects were free of identifiable medical disease. Two elderly women had mild diabetes mellitus that developed during adulthood and was treated with diet in one and with an oral hypoglycemic agent in the other. One elderly man had hyperlipidemia that was treated with diet.

Protocol: A dose of 180 to 300 mg of quinidine base, as the lactate salt, was dissolved in 50 ml of a solution of 5 percent dextrose in water and infused into an antecubital vein for 15 minutes with a constant rate infusion pump during continuous electrocardiographic monitoring. Multiple venous blood samples were drawn from the contralateral arm before the infusion and at the following

hours after the start of the infusion: 0.25, 0.375, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24 and 30. An additional sample was drawn 18 hours after the infusion in the young subjects. All urine was collected within 48 hours after the start of the infusion in samples divided as follows: 0 to 4, 4 to 8, 8 to 24 and 24 to 48 hours. Serum and aliquots of urine were frozen until the time of assay.

Quinidine and pharmacokinetic measurements: *Quinidine concentrations in all serum and urine samples* were determined with a modification of the double extraction spectrophotofluorometric technique.[7] The technique has a sensitivity limit of at least 0.03 μg/ml and a coefficient of variation for identical samples of 3 percent or less; it is essentially specific for unchanged quinidine and for dihydro-

TABLE I

Subject Characteristics and Pharmacokinetic Variables for Quinidine

	Young Subjects (no. = 14) (mean ± SE)		Elderly Subjects (no. = 8) (mean ± SE)		Value of Student's Independent *t* Test	Level of Significance*
Subject characteristics						
Age (yr)	28.9	±0.8	65.5	±1.0	28.9	$P < 0.001$
Sex (M/F)	7/7	...	5/3	...	...	...
Weight (kg)	68.0	±2.7	83.4	±5.9	2.74	$P < 0.025$
Serum albumin concentration (g/100 ml)	4.41	±0.06	4.33	±0.08	0.87	NS
Creatinine clearance (ml/min per kg)	1.57	±0.07	1.11	±0.11	3.52	$P < 0.005$
Pharmacokinetic variables for quinidine						
V_1 (liters/kg)	0.52	±0.10	0.26	±0.04	1.99	$0.05 < P < 0.1$
V_d (liters/kg)	2.39	±0.18	2.18	±0.22	0.75	NS
$t_{1/2\alpha}$ (min)	2.69	±0.65	2.57	±0.24	0.14	NS
$t_{1/2\beta}$ (hours)	7.25	±0.71	9.70	±0.86	2.13	$P < 0.05$
Total clearance (ml/min per kg)	4.04	±0.30	2.64	±0.23	3.21	$P < 0.005$
Renal clearance (ml/min per kg)	1.43	±0.13	0.99	±0.12	2.29	$P < 0.05$
Mean percent unbound quinidine	24.6	±0.9	28.2	±2.6	1.57	NS

* d.f. (degrees of freedom) = 20 by two-tailed test.
NS = not significant; *P* = probability; SE = standard error of the mean; $t_{1/2\alpha}$ = apparent distribution half-life; $t_{1/2\beta}$ = apparent elimination half-life; V_1 = volume of the central compartment; V_d = total volume of distribution.

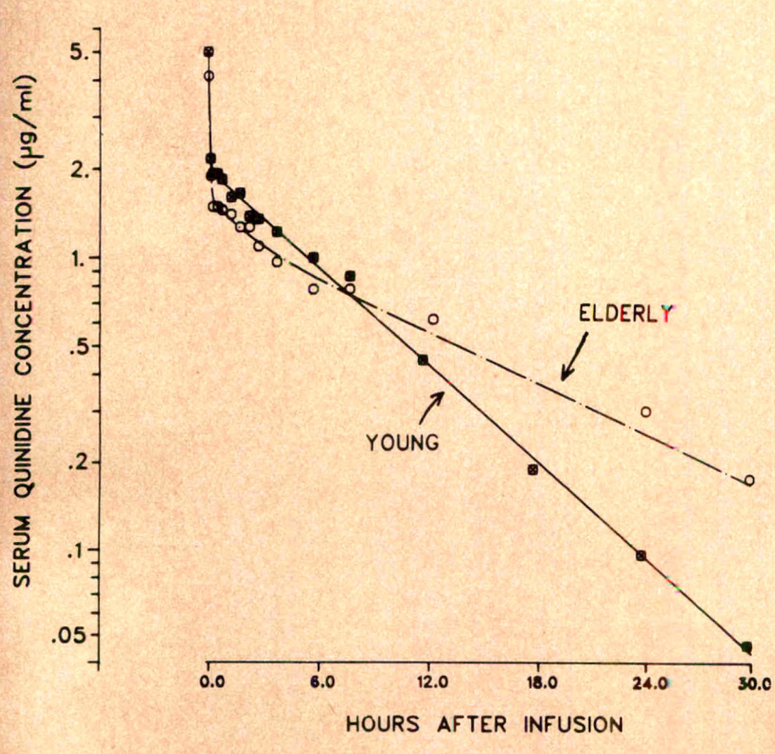

FIGURE 1. Serum quinidine concentrations and computer-determined pharmacokinetic functions for representative young and elderly male volunteers.

quinidine, a pharmacologically active impurity.[8–11] This method may also quantitate, in part, a pharmacologically active hydroxylated quinidine metabolite present in relatively low concentrations in the serum of some patients receiving long-term quinidine therapy.[12] The relevance of this metabolite in single dose studies is not known.

The extent of quinidine binding to serum protein in all samples was determined with a modification of the equilibrium dialysis technique of Hughes et al.[13] Quinidine protein-binding for each subject was expressed as the across-sample mean percent of unbound quinidine in all specimens drawn from that subject over the course of the study.

Postinfusion serum quinidine concentrations were analyzed with iterative nonlinear least-squares regression analysis.[7,14,15] The data were fitted to the sum of the smallest number of exponential terms necessary to describe the points adequately. The fitted functions were used to calculate the following pharmacokinetic variables[7,16–18]: volume of the central compartment (V_1), total volume of distribution (V_d), apparent distribution half-life ($t_{1/2\alpha}$), apparent elimination half-life ($t_{1/2\beta}$) and total clearance rate. The "projected" cumulative excretion of quinidine was determined with the 48 hour excretion value together with a semilogarithmic plot of excretion rate versus the mid point of the collection interval. The renal clearance of quinidine was calculated as the product of total clearance and the projected cumulative fraction of the dose excreted in the urine.

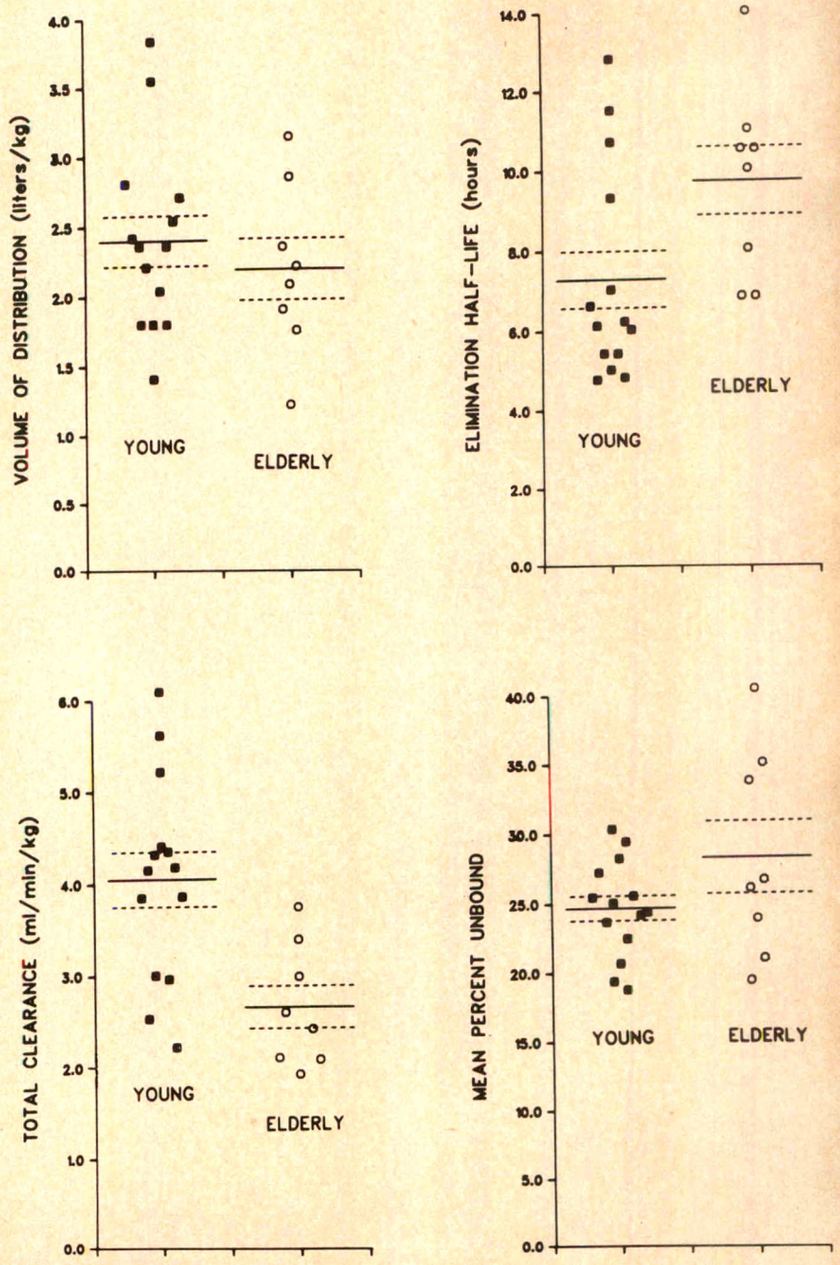

FIGURE 2. Individual and mean (± standard error) values of pharmacokinetic variables for quinidine in young and elderly subjects. See Table I for statistical analysis.

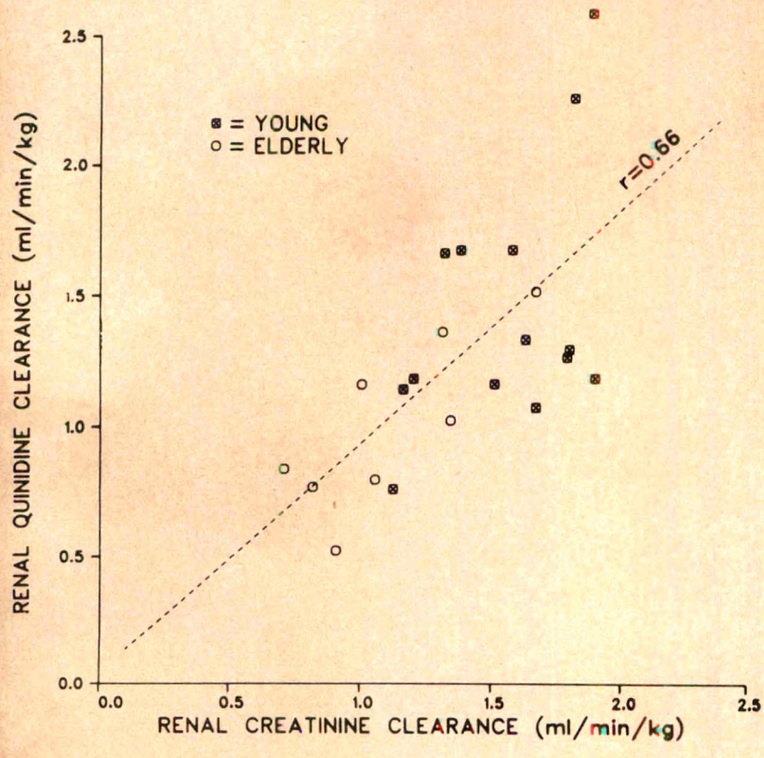

FIGURE 3. Overall relation of renal clearance of quinidine to that of creatinine. Also shown is the least-squares regression line that indicates highly significant correlation between the two ($r = 0.66$, $P < 0.001$).

Differences in kinetic variables between the young and elderly subjects were assessed with Student's two-tailed t test for independent samples.

Results

No important adverse clinical effects were associated with the intravenous infusion of quinidine. Postinfusion serum quinidine concentration decreased in bi- or triexponential fashion in 20 of the 22 subjects. Two subjects (one elderly man and one young woman) had only a single exponential disappearance pattern. Figure 1 shows representative serum concentration curves.

Central compartment volumes tended to be smaller in the elderly subjects than in the young (Table I), but the difference was only of borderline significance. No differences between the groups were evident in the apparent distribution half-life ($t_{1/2\alpha}$) or in the total apparent volume of quinidine distribution (Fig. 2). However, in the elderly, the apparent elimination half-life of quinidine ($t_{1/2\beta}$) was significantly longer and total quinidine clearance was significantly lower than in the young subjects (Table I, Fig. 2). Renal clearance of both creatinine and quinidine was lower in the elderly, and the renal clearance of creatinine and quinidine correlated significantly ($r = 0.66$, $P < 0.001$) (Fig. 3). However, in both groups renal clearance averaged only about 35 to 40 percent of the rate of total quinidine clearance, confirming that extrarenal elimination mechanisms (presumably hepatic biotransformation) constitute the major route of quinidine clearance. Finally, protein-binding of quinidine tended to be less in the elderly than in the young subjects. However, the difference was not significant and was not associated with a difference between groups in serum albumin concentration.

Discussion

This study demonstrates a significant prolongation of the elimination half-life of quinidine and a reduction of its total clearance in subjects aged 60 years or older compared with values in subjects aged 34 years or less. Renal clearance of creatinine and quinidine were lower in the elderly and were highly correlated. However, in both groups extrarenal clearance—presumably as a result of hepatic biotransformation—was the more important route of elimination. If our assay for quinidine in urine also quantitated some quinidine metabolites, then renal clearance of intact quinidine in both groups would be even lower than we estimated. There was no evidence that a subject's age affected the distribution of quinidine, although the extent of binding to serum protein tended to be decreased in the elderly.

Implications: Our findings suggest that hepatic biotransformation and renal excretion of quinidine decrease with age. Similar age-dependent changes in pharmacokinetics have been described for several drugs.[3–6] The choice of quinidine dose schedules in clinical practice should take into account the age of the patient. A decrease in quinidine clearance in the elderly could predispose to excessive drug accumulation and possibly toxicity unless doses are appropriately adjusted.

Acknowledgment

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References

1. **Holloway DA:** Drug problems in the geriatric patient. Drug Intel Clin Pharm 8:632–642, 1974
2. **Greenblatt DJ, Allen MD, Shader RI:** Toxicity of high-dose flurazepam in the elderly. Clin Pharmacol Ther 21:355–361, 1977
3. **Crooks J, O'Malley K, Stevenson IH:** Pharmacokinetics in the elderly. Clin Pharmacokinet 1:280–296, 1976
4. **Triggs EJ, Nation RL:** Pharmacokinetics in the aged: a review. J Pharmacokinet Biopharm 3:387–418, 1975
5. **Richey DP, Bender AD:** Pharmacokinetic consequences of aging. Ann Rev Pharmacol Toxicol 17:49–65, 1977
6. **Shader RI, Greenblatt DJ, Harmatz JS, et al:** Absorption and disposition of chlordiazepoxide in young and elderly male volunteers. J Clin Pharmacol 17:709–718, 1977
7. **Greenblatt DJ, Pfeifer HJ, Ochs HR, et al:** Pharmacokinetics of quinidine in humans after intravenous, intramuscular and oral administration. J Pharmacol Exp Ther 202:365–378, 1977
8. **Midha KK, Charette C:** GLC determination of quinidine from plasma and whole blood. J Pharm Sci 63:1244–1247, 1974
9. **Valentine JL, Driscoll P, Hamburg EL, et al:** GLC determination of quinidines in human plasma. J Pharm Sci 65:96–98, 1976
10. **Huffman DH, Hignite CE:** Serum quinidine concentrations: comparison of fluorescence, gas-chromatographic, and gas-chromatographic/mass-spectrometric methods. Clin Chem 22:810–812, 1976
11. **Midha KK, McGilveray IJ, Charette C, et al:** Comparison of a spectrofluorometric method with a gas-liquid chromatographic procedure for the determination of quinidine plasma levels. Can J Pharm Sci 12:41–44, 1977
12. **Drayer DE, Restivo K, Reidenberg MM:** Specific determination of quinidine and (3S)-3-hydroxyquinidine in human serum by high-pressure liquid chromatography. J Lab Clin Med 90:816–822, 1977
13. **Hughes IE, Ilett KG, Jellett LB:** The distribution of quinidine in human blood. Br J Clin Pharmacol 2:521–525, 1975
14. **Usanis RA:** NLIN–nonlinear least squares estimation of parameters (Library Services Series Document no. LSR-089-1). Research Triangle Park, NC, Triangle Universities Computation Center, 1972
15. **Marquardt DW:** An algorithm for least-squares estimation of nonlinear parameters. J Soc Ind Appl Math 11:431–441, 1963
16. **Greenblatt DJ, Koch-Weser J:** Clinical pharmacokinetics. N Engl J Med 293:702–705, 964–970, 1975
17. **Gibaldi M, Perrier D:** Pharmacokinetics. New York, Marcel Dekker, 1975
18. **Wagner JG:** Fundamentals of Clinical Pharmacokinetics. Hamilton, Illinois, Drug Intelligence Publications, 1975

Efficacy of Lidocaine in Preventing Primary Ventricular Fibrillation Within 1 Hour After a 300 mg Intramuscular Injection

A Double-Blind, Randomized Study of 300 Hospitalized Patients With Acute Myocardial Infarction

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The effectiveness of intramuscular lidocaine in preventing in-hospital primary ventricular fibrillation within 1 hour after injection of the drug in patients with acute myocardial infarction was assessed in a double-blind randomized study performed in 300 such patients admitted within 6 hours of myocardial infarction. Six of 147 patients treated with 300 mg of intramuscular lidocaine had ventricular fibrillation compared with 4 of 153 control subjects. The lidocaine blood level of the patients who experienced ventricular fibrillation was 1.4 ± 0.7 μg/ml (mean ± standard deviation) at the time of fibrillation, a value not significantly different from that of treated patients who did not experience fibrillation. Lidocaine blood levels in the latter were 1.9 ± 1.1, 2.1 ± 1.1, 2.1 ± 1.1 and 1.7 ± 0.7 μg/ml, respectively, 7, 15, 30 and 60 minutes after injection. In this study intramuscular lidocaine was ineffective in preventing ventricular fibrillation, possibly because the given dose, 300 mg, prevented attainment of adequate blood levels of the drug.

Seventy percent of the total mortality due to acute myocardial infarction occurs outside the hospital, presumably as a consequence of primary ventricular fibrillation.[1] Therefore, a safe and effective drug that can be given as a prophylactic measure outside the hospital is needed. The efficacy of intravenous lidocaine in preventing in-hospital primary ventricular fibrillation has been established.[2] However, because intravenous administration of lidocaine is often not feasible or practical outside the hospital, several studies[3–6] have been performed to evaluate the effect of intramuscular administration of this drug. In these studies, intramuscular lidocaine in a dose of 250 to 300 mg or 4.5 mg/kg body weight was shown to reduce ventricular ectopic activity. Another study[7] reported a lower rate of early death outside the hospital after intramuscular injection of 300 mg of lidocaine in subjects with acute myocardial infarction; however, neither acute myocardial infarction nor primary ventricular fibrillation was adequately documented. To ensure such documentation, we devised a double-blind controlled study of the effectiveness of intramuscular lidocaine in hospitalized patients after acute infarction.

Material and Method

Patients: The study was performed in patients under the age of 70 years, admitted to the hospital within 6 hours after the onset of symptoms of acute myocardial infarction. The diagnosis of infarction was based on a characteristic history of chest pain correlated with typical electrocardiographic changes (new Q waves and loss of R wave voltage) and a serial rise in serum enzyme values (creatine kinase [CK], serum glutamic oxaloacetic transaminase [SGOT] and lactic dehydrogenase [LDH]). Continuous electrocardiographic monitoring was performed in all patients during their stay in the coronary care unit. Infarct size was estimated by sampling serum enzymes (SGOT) at 6 hour intervals until the peak value was reached. Infarct location was defined according to the criteria proposed by the New York Heart Association.[8]

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Patients were excluded from the study if on admission they had bradycardia with a ventricular rate of less than 50 beats/min, pulmonary congestion, complete atrioventricular block, persistent ventricular tachycardia or ventricular fibrillation.

From May 1975 to September 1977, a total of 911 patients were admitted consecutively to the coronary care unit with the diagnosis of probable acute myocardial infarction; 321 patients met the criteria for the study and entered the trial.

Twenty-one patients were withdrawn from the study because the diagnosis of acute myocardial infarction could not be proved with serial enzyme studies. Of the remaining 300 patients, 147 received 300 mg of lidocaine and 153 received a solution of 0.65 percent sodium chloride and water. The two groups were comparable with respect to age, sex, site and size of infarction and time of hospital admission (Table I).

Protocol: Immediately after admission, randomized patients received an intramuscular injection of 300 mg lidocaine in a 10 percent solution or 0.65 percent sodium chloride and water in the deltoid muscle of one arm. The injection site was massaged vigorously for 1 minute. The nature of the injected solution was unknown to the medical and nursing staff. Blood samples from the antecubital vein of the other arm were taken 7, 15, 30 and 60 minutes after injection. In addition, blood samples were also taken as soon as possible after the occurrence of primary ventricular fibrillation. Blood levels of lidocaine were determined with gas chromatography.[9] The study was terminated within 1 hour after the intramuscular injection or if primary ventricular fibrillation or a sustained ventricular tachycardia occurred within that period. Differences in incidence were tested with the chi-square test, differences in blood lidocaine levels with Student's *t* test.

Results

The incidence of major ventricular arrhythmias in the first 60 minutes after injection of lidocaine or sodium chloride and the mortality rate were equal in both the treated and control groups (Table II). In the treated group primary ventricular fibrillation and ventricular tachycardia occurred in seven patients 15, 17, 20, 30, 35, 40 and 45 minutes, respectively, after the intramuscular injection. Blood lidocaine levels of five treated patients with ventricular fibrillation were 0.8, 0.9, 1.1, 2.1 and 2.2 μg/ml, respectively (mean ± standard deviation 1.4 ± 0.7). The patient in the treated group who had ventricular tachycardia had a plasma lidocaine level of 0.9 μg/ml. The blood samples were drawn within 3 minutes after onset of the arrhythmia. In one patient with recurrent ventricular fibrillation blood sampling failed. The mean blood lidocaine levels of treated patients who had no fibrillation measured 1.9 ± 1.1, 2.1 ± 1.1, 2.1 ± 1.1 and 1.7 ± 0.7 μg/ml, respectively, 7, 15, 30 and 60 minutes after injection (Fig. 1). The blood levels of the patients who experienced fibrillation were not significantly lower than these values.

Lidocaine caused no major side effects such as respiratory arrest or epileptic seizures. Nine patients showed drowsiness, numbness of tongue and lips or speech disturbances and dizziness. All deaths occurred after termination of the trial.

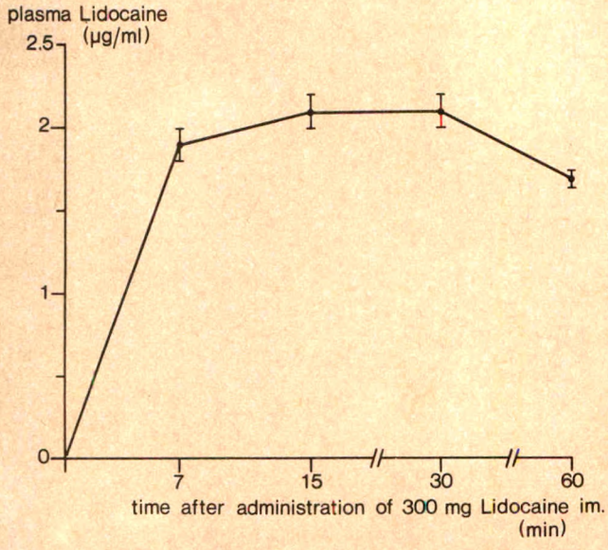

FIGURE 1. Plasma lidocaine levels (mean values ± standard error of the mean) in 140 of the 147 patients of the treated group. im. = intramuscularly.

TABLE I

Clinical Features of 300 Patients With Acute Myocardial Infarction

	Treated Group (no. = 147)	Control Group (no. = 153)
Mean age (yr)	58.8	57.1
Sex		
Male	118	117
Female	29	36
Site of infarction		
Anterior	70	78
Inferior	72	70
Anterior and inferior	1	3
Undetermined	4	2
Mean peak SGOT (IU)	123	120
Admission time (hr)*		
0–2	69	73
2–4	56	58
4–6	22	22

* Time interval between onset of symptoms and arrival in the coronary care unit.
SGOT = serum glutamic oxaloacetic transaminase.

Discussion

Intramuscular lidocaine in a dose of 300 mg given in the deltoid muscle was ineffective in preventing primary

TABLE II

Mortality and Incidence of Major Ventricular Arrhythmias Within 60 Minutes After Injection of Lidocaine or Sodium Chloride

	Treated Group (no. = 147)	Control Group (no. = 153)
Arrhythmias		
Primary ventricular fibrillation	6	4
Ventricular tachycardia	1	2
Deaths		
Cardiac rupture	1	2
Cardiogenic shock	4	3
Pulmonary edema	0	1

ventricular fibrillation within 1 hour of injection in our patients with a diagnosis of acute myocardial infarction. In this special clinical setting several mechanisms might be responsible for this ineffectiveness.

Inadequate drug dose and blood levels: The failure of this drug regimen may have been primarily due to an inadequate dose. The blood lidocaine levels of patients in the treated group, particularly of those who experienced fibrillation, (Fig. 1) were at the low end of the reported therapeutic range of 2 to 5 μg/ml.[10] However, this reported therapeutic range[10] is based on data on the effectiveness of lidocaine in suppressing ventricular ectopic beats only, and a dose that effectively suppresses such beats may be ineffective in preventing primary ventricular fibrillation.[11] A larger lidocaine dose seems to be required to prevent primary ventricular fibrillation than to suppress ventricular ectopic beats.[2]

Early versus later arrhythmias in acute infarction: Another explanation for the failure of lidocaine to prevent fibrillation might be that the mechanism of arrhythmias in the earliest phase of myocardial infarction is different from that in later stages.[12] In the experimental model of Harris[13] an early phase of arrhythmias occurred within minutes after coronary arterial occlusion. After several hours a second phase occurred, lasting until 24 to 48 hours after occlusion. There is evidence that the early arrythmias are primarily due to reentry within the ischemic myocardium,[12,14–16] and drugs might be ineffective in suppressing these early arrhythmias because adequate concentrations cannot be attained within the nonperfused ischemic myocardium. The later arrhythmias are thought to be primarily due to increased automaticity, and also to reentry, within the subendocardial Purkinje system. In this tissue, adequate drug concentrations might be achieved with diffusion by way of the cavitary blood. It is not known whether in man a similar distinction exists between these two phases of arrhythmias. One clinical study[17] reported that lidocaine was unable to suppress ventricular arrhythmias occurring within 1 hour of myocardial infarction; in another,[18] lidocaine abolished ventricular arrhythmias within the first hour in 89 percent of cases. Neither study revealed whether the failure of lidocaine to suppress early ischemic arrhythmias was due to differences in arrhythmogenic mechanism of early and late arrhythmias or to ineffective plasma levels of the drug.

Our patients who experienced primary ventricular fibrillation did so between 1/2 and 2 hours after the onset of symptoms. We cannot say whether their arrhythmia was "early" or "late." However, we believe that failure to achieve adequate plasma levels by intramuscular injection of lidocaine in the early phase of myocardial infarction is an important factor in explaining the effectiveness of the drug. It may even be that low plasma levels of lidocaine may be deleterious because lidocaine in small doses can enhance reentrant rhythms.[19–21]

Implications: Our results suggest that prophylactic administration of 300 mg of lidocaine intramuscularly should not be recommended for every patient suspected of having an acute myocardial infarction. On the other hand, further studies using larger doses are needed to clarify the efficacy of intramuscular lidocaine in preventing primary ventricular fibrillation after infarction.

References

1. **Kuller L, Cooper M, Perper J:** Epidemiology of sudden death. Arch Intern Med 129:714–719, 1972
2. **Lie KI, Wellens HJ, van Capelle FJ, et al:** Lidocaine in the prevention of primary ventricular fibrillation. A double-blind randomized study of 212 consecutive patients. N Engl J Med 291:1324–1326, 1974
3. **Bellet S, Roman L, Kostis JB, et al:** Intramuscular lidocaine in the therapy of ventricular arrhythmias. Am J Cardiol 27:291–293, 1972
4. **Bernstein V, Bernstein M, Griffiths J, et al:** Lidocaine intramuscularly in acute myocardial infarction. JAMA 219:1027–1031, 1972
5. **Fehmers MCO, Dunning AJ:** Intramuscularly and orally administered lidocaine in the treatment of ventricular arrhythmias in acute myocardial infarction. Am J Cardiol 29:514–519, 1972
6. **Singh JB, Kocot SL:** A controlled trial of intramuscular lidocaine in the prevention of premature ventricular contractions associated with acute myocardial infarction. Am Heart J 91:430–436, 1976
7. **Valentine PA, Frew JL, Mashord ML, et al:** Lidocaine in the prevention of sudden death in the pre-hospital phase of acute infarction. N Engl J Med 291:1327–1331, 1974
8. Criteria Committee of the New York Heart Association: Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels, seventh edition. Boston, Little, Brown, 1973, p 98
9. **Svinhufvud G, Örtengren B, Jacobsen SE:** The estimation of lidocaine and prilocaine in biological material by gas chromatography. Scand J Clin Lab Invest 17:162–164, 1965
10. **Arnsdorf MF:** Electrophysiologic properties of antidysrhythmic drugs as a rational basis for therapy. Med Clin North Am 60: 213–232, 1976
11. **Darby S, Bennet MA, Cruickshank JC, et al:** Trial of combined intramuscular and intravenous lignocaine in prophylaxis of ventricular tachyarrhythmias. Lancet 1:817–819, 1972
12. **Bigger JT, Dresdale RJ, Heissenbuttel RH, et al:** Ventricular arrhythmias in ischemic heart disease: mechanism, prevalence, significance and management. Prog Cardiovasc Dis 19:255–300, 1977
13. **Harris AS:** Delayed development of ventricular ectopic rhythms following experimental coronary occlusion. Circulation 1: 1318–1328, 1950
14. **Scherlag BJ, El Sherif N, Hope RP, et al:** Characterization and localization of ventricular arrhythmias resulting from ischemia and infarction. Circ Res 35:372–383, 1974
15. **Downar E, Janse MJ, Durrer D:** The effect of ischemic blood transmembrane potential of normal porcine ventricular myocardium. Circulation 55:455–463, 1977
16. **Wit AL, Friedman PL:** Basis for ventricular arrhythmias accompanying myocardial infarction: alterations in electrical activity of ventricular and Purkinje fibers after coronary artery occlusion. Arch Intern Med 135:459–472, 1975
17. **Adgey AAJ, Allen JP, Geddes JS, et al:** Acute phase of myocardial infarction. Lancet 2:501–504, 1971
18. **Goldreyer BN, Wyman MG:** The effect of first hour hospitalization in myocardial infarction (abstr). Circulation 50:Suppl III:III-121, 1974
19. **Geddes JS, Webb S, Pantridge JF:** Limitations of lignocaine in control of early ventricular dysrhythmias complicating acute myocardial infarction. Br Heart J 34:964–965, 1972
20. **Gamble OW, Cohn K:** Effect of propranolol, procainamide and lidocaine on ventricular automaticity and reentry in experimental myocardial infarction. Circulation 46:498–506, 1972
21. **Lazzara, R, Hope RR, El-Sherif N, et al:** Effects of lidocaine on hypoxic and ischemic cardiac cells. Am J Cardiol 41:872–879, 1978

Natural History of Myocardial Infarction in the Coronary Drug Project: Long-Term Prognostic Importance of Serum Lipid Levels

CORONARY DRUG PROJECT
RESEARCH GROUP*

The relation between baseline fasting serum lipid levels (serum cholesterol and triglycerides) and 5 year rates for four end points—mortality from all causes, mortality from coronary heart disease, sudden death due to coronary heart disease and incidence of nonfatal myocardial infarction plus coronary death—was studied in 2,789 men. These were patients in the Coronary Drug Project placebo group who were 30 to 64 years old on entry and had recovered from one or more previous documented myocardial infarctions. Serum cholesterol was significantly related to all four end points, in both univariate and multivariate regression analyses (with control of 38 or 39 other factors in the latter). This significant relation of cholesterol to these end points was shown at low, medium and high levels of serum triglycerides. In contrast, baseline fasting serum triglyceride levels were not positively related to any of these end points. In these postmyocardial infarction patients, findings indicative of cardiovascular status at baseline evaluation, particularly the state of the myocardium, were more powerful prognosticators than serum cholesterol. These findings underscore the importance of efforts to prevent the *first* coronary episode. They also indicate the possibility after recovery from acute myocardial infarction of improving long-term prognosis through reduction of serum cholesterol.

The Coronary Drug Project—a nationwide collaborative study sponsored by the National Heart, Lung, and Blood Institute—was designed to assess the long-term efficacy of drugs influencing lipid metabolism in men surviving one or more episodes of myocardial infarction.[1–5] Because this objective required more than 8,000 patients and random assignment to a placebo group, the Coronary Drug Project also provided a unique opportunity to study the long-term clinical course and prognosis after recovery from myocardial infarction.

This report is one of a series from the Coronary Drug Project.[6–11] Previous papers presented data indicating that in persons recovered from myocardial infarction, the most powerful factors related to long-term prognosis are those reflecting the status of the myocardium—for example, S-T segment depression or Q waves in the postrecovery resting electrocardiogram, electrocardiographic evidence of ventricular conduction defects, premature ventricular complexes or tachycardia and cardiomegaly on chest X-ray film.[6–9] Within this context, it remains of great theoretical and practical concern whether—and to what extent—such treatable risk factors as hyperlipidemia, cigarette smoking and hypertension continue to relate to prognosis after myocardial infarction. This study deals with one set among these variables—serum lipids (cholesterol and triglycerides) and their relation to long-term prognosis. Many research reports demonstrate that susceptibility to a

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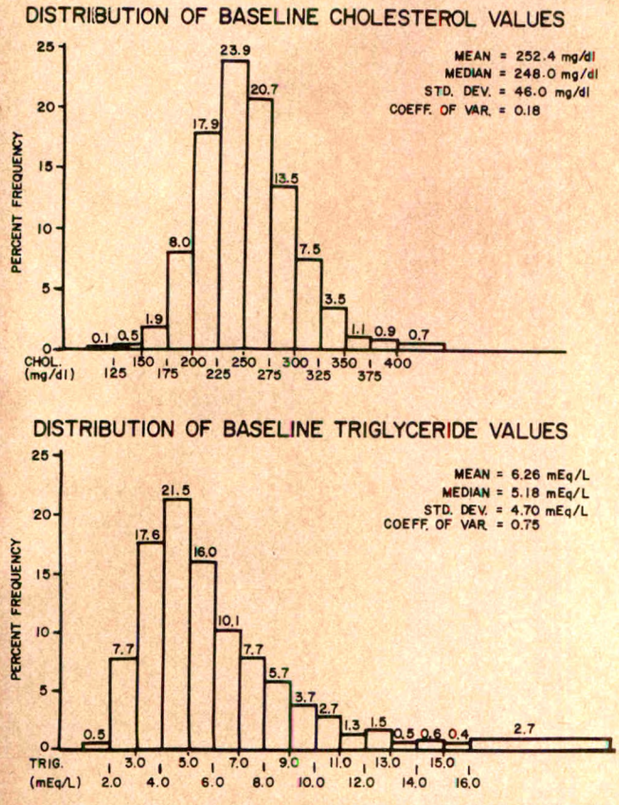

FIGURE 1. Relative frequency distributions of baseline serum cholesterol levels and fasting triglyceride levels for the 2,789 men of the Coronary Drug Project placebo group. The cholesterol and triglyceride values shown are the means, for each man, of three baseline determinations at 4 week intervals. CHOL. = cholesterol; COEFF. OF VAR. = coefficient of variation; L = liter; STD. DEV. = standard deviation; TRIG. = triglycerides.

first episode of premature coronary heart disease in men is directly and independently related to serum cholesterol level.[12–38] In contrast, there is little information on the long-term prognostic significance of serum cholesterol concentration in persons recovered from one or more episodes of frank clinical coronary heart disease.[39–42] To our knowledge, there are no published reports on the relation of fasting serum triglycerides to the prognosis of such patients. This study utilized the 5 year follow-up experience of the 2,789 men in the placebo group of the Coronary Drug Project to evaluate these relations.

Method

Patients: The background, design and organization of the Coronary Drug Project were described in detail in earlier reports.[1–11] The project's primary objective was to test the efficacy and safety of several lipid-influencing drugs in the long-term therapy of coronary heart disease in men with proved previous myocardial infarction.[1–5] For this purpose, 8,341 patients were recruited by the 53 participating clinical centers and randomly assigned to six groups. Approximately one third of the patients—2,789 men—were allocated to the placebo group. Their 5 year experience is the basis of this report on the relation of prognosis to serum lipid levels obtained before randomization.

Patients accepted into the Coronary Drug Project were men aged 30 to 64 years who had documented evidence of one or more myocardial infarctions, were considered on entry to be in functional class I or II (New York Heart Association classification)[43] and were free from a specified list of excluding diseases and conditions.[1] All patients had had their latest myocardial infarction at least 3 months earlier, and all were free of evidence of recent worsening of coronary disease or other major illnesses. In a series of standardized baseline examinations, extensive data—including demographic, clinical, electrocardiographic and biochemical information—were collected for all patients. These included three determinations of serum cholesterol and triglycerides at 1 month intervals.

Serum lipid determinations: For these chemical measurements, all men were given detailed instructions to report to the clinic in the morning in the fasting state, having taken no food or drink for at least 12 hours and having consumed no alcohol the evening before. Frozen serum packed in dry ice was transmitted to the Coronary Drug Project's Central Laboratory, Center for Disease Control, Atlanta, Georgia. It was analyzed for serum cholesterol by a semiautomated modification of the Abell-Kendall method and for triglycerides by the Lofland modification of the Van Handel-Zilversmit method.[1,44–46] Technical errors (T.E.) of the analytical procedures were estimated from data on split pairs of sera, with use of the formula, $T.E. = \sqrt{\Sigma d^2/2N}$, where d is the difference in analytical value of a split pair and N is the number of pairs, as determined by the Coronary Drug Project's external laboratory surveillance program, carried out with the Central Laboratory blinded. They were in the order of 5.0 mg/dl and 0.35 mEq/liter for serum cholesterol and triglycerides, respectively, with resultant coefficients of variation of approximately 2 and 7 percent, respectively; that is, the serum cholesterol analytical method was consistently more reproducible than the serum triglyceride method. For evaluation of the relation between serum lipids and long-term prognosis, the mean of the three baseline determinations of serum cholesterol and triglycerides, respectively, was taken as the single baseline value for each of the 2,789 men in the placebo group.

Follow-up: All men reported to the clinic for an interval visit every 4 months. A general examination, including a resting electrocardiogram, was made annually. Complaints and findings suggestive of illness or of drug toxicity were thoroughly evaluated by the research clinic. Data in a standard format were sent to the Coordinating Center from the clinics and were serially monitored for "events" including death, recurrent myocardial infarction, intermediate coronary episodes called acute coronary insufficiency, angina pectoris, electrocardiographic findings, stroke, venous thromboembolism and other findings.

Statistical analysis: This report is based on data available through September 30, 1974. As of that date, all 2,789 men in the placebo group had been under observation for at least 54 months, and 96 percent for at least 60 months. The data were evaluated to assess the relation at baseline between serum lipids and other variables, as well as the relation of serum lipids to prognosis for this cohort over the 5 year period. For these latter analyses, four end points were used—mortality from all causes, coronary heart disease mortality, sudden coronary death (coronary death occurring within 60 minutes of onset of symptoms) and incidence of recurrent major coronary events (defined as definite nonfatal myocardial infarction plus fatal coronary events).

The primary statistical tool used to assess the relation between serum lipids and prognosis was the linear regression method.[6–11] It was first applied to each lipid variable singly; that is, independently of all other variables. Second, the two

lipid variables were considered simultaneously. Each lipid variable was then analyzed simultaneously with 38 other baseline characteristics (demographic, clinical, electrocardiographic, biochemical, hematologic, pharmacologic), including key prognosticators related to the status of the myocardium and arterial vasculature.[6] In all analyses, t values were computed and quantile analyses were also performed.

Results

Baseline serum lipid distributions and relations to other variables: The distributions of baseline serum cholesterol and triglyceride levels for the cohort of 2,789 placebo patients are presented in Figure 1. For triglycerides, the distribution is markedly skewed to the right, and its coefficient of variation is much greater than that for cholesterol.

Detailed analyses of the relation between serum cholesterol and other baseline factors, of possible prognostic importance after a myocardial infarction, showed most correlations to be of low order or nil, except for the expected sizeable positive association between cholesterol and triglycerides (0.37). Similar data for serum triglycerides showed the largest correlations to be between this variable and fasting plasma glucose (0.16), post-challenge plasma glucose (0.22), serum uric

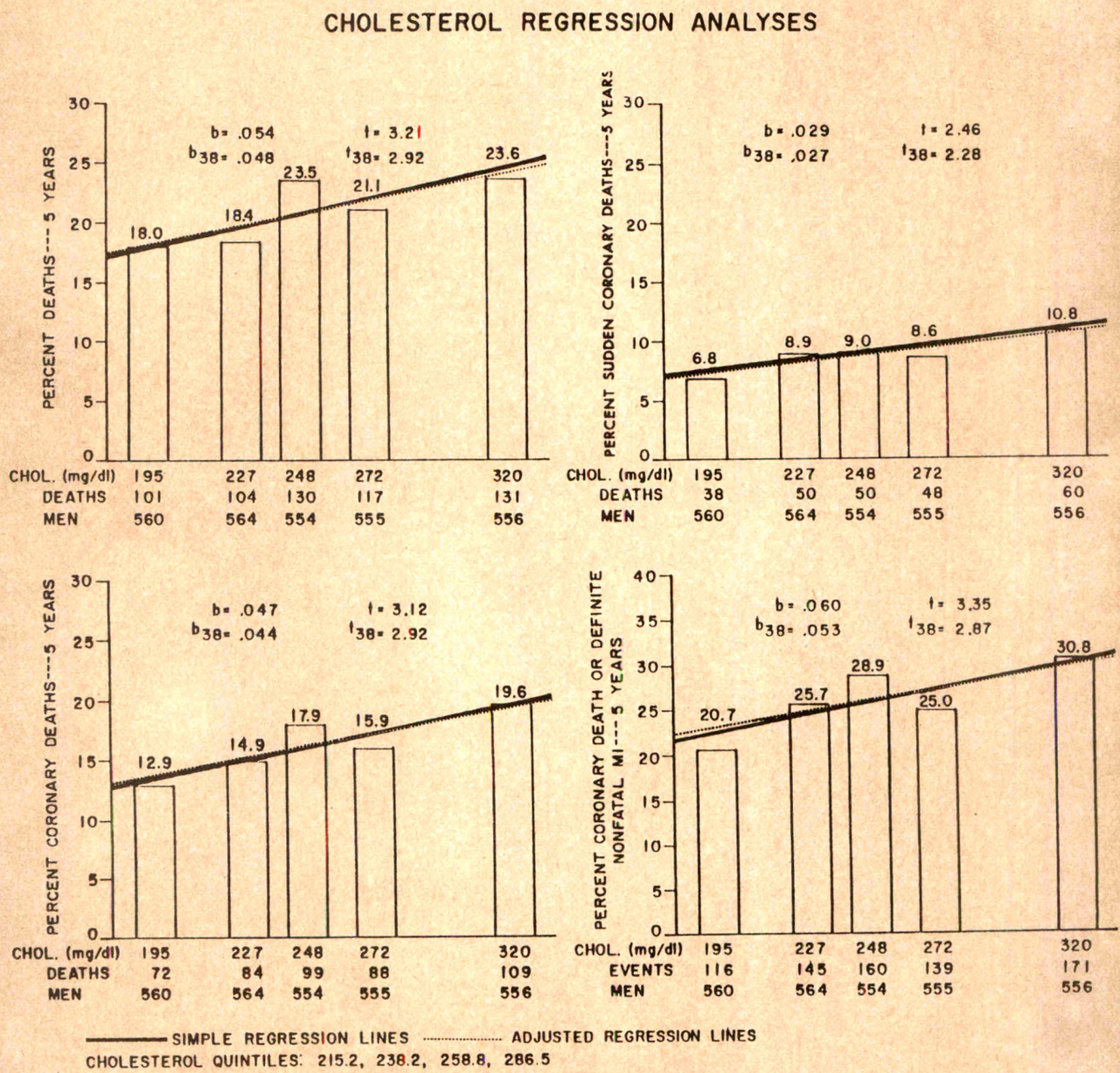

FIGURE 2. Analyses of relations between baseline serum cholesterol (CHOL.) levels and 5 year rates for four stipulated end points for the 2,789 men studied. The two slopes in each graph are, respectively, the univariate and multivariate linear regression lines for the relation between serum cholesterol and the indicated end point. For the multivariate regression line, adjustment is made for the influence of 38 other baseline variables on risk of the event. MI = myocardial infarction.

acid (0.17) and relative body weight (0.19), in addition to the previously noted correlation with cholesterol.

Prognostic significance of baseline serum lipid levels: For the four end points evaluated—mortality from all causes, coronary heart disease mortality, sudden coronary death and incidence of major coronary events (nonfatal myocardial infarction and coronary death)—the numbers of events were 583, 452, 246 and 731, respectively, and the 5 year rates were 20.9, 16.2, 8.8 and 26.2 percent, respectively.

With 5 year mortality from all causes as the end point and 40 baseline variables included in the stepwise linear regression analysis,[6] cholesterol was the ninth variable selected, after eight others, all related to the status of the myocardium and the arterial vasculature. In order these were: S-T segment depression, cardiomegaly on chest X-ray film, New York Heart Association functional class, heart rate, ventricular conduction defects, history of diuretic use, number of myocardial infarctions and history of intermittent claudication. The adjusted t value, taking account of the 39 other variables in the analysis, was 3.64 for cholesterol, compared with the univariate unadjusted t value of 3.23; that is, the relation of baseline serum cholesterol to 5 year risk of death

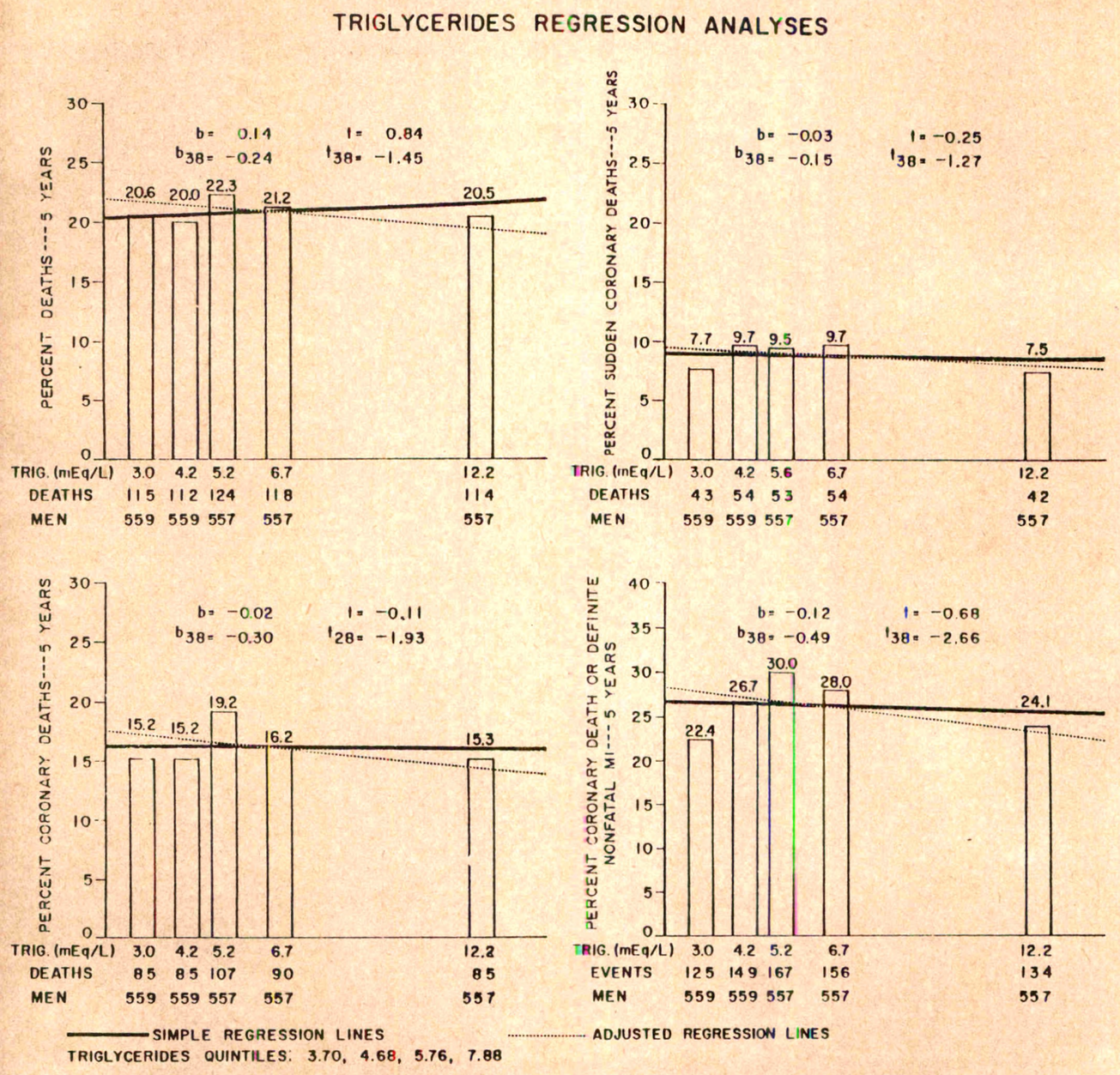

FIGURE 3. Analyses of relations between baseline serum fasting triglyceride (TRIG.) levels and 5 year rates for four stipulated end points for the 2,789 men studied. The two slopes in each graph are, respectively, the univariate and multivariate linear regression lines for the relation between serum triglycerides and the indicated end point. For the multivariate regression line, adjustment is made for the influence of 38 other baseline variables on risk of the event. L = liter; MI = mycardial infarction.

was highly significant, independent of other variables. For the triglycerides, the 14th variable selected, the unadjusted t value was 0.84, the adjusted t value −2.61; that is, there was no evidence of a positive association between baseline fasting serum triglycerides and 5 year risk of death in either univariate or multivariate analyses.

Figure 2 summarizes the findings on the relation between mean serum cholesterol at entry and the four end points. Clearly, a significant and consistent relation was recorded with both univariate and multivariate analyses. For mortality from all causes, the value for the slope (b = 0.054) indicates that for a man in this study with a baseline average serum cholesterol level 100 mg/dl higher than that of another man, the risk of mortality in 5 years increased by 5.4 percentage points. Thus, a man with a serum cholesterol level of 200 mg/dl at entry had about an 18 percent probability of dying in 5 years and a man with a level of 300 mg/dl, a probability of about 23 percent—about 30 percent greater. (A similar result was obtained when the multivariate analysis encompassed 39, rather than 38 adjusting factors, including serum triglycerides. In that case, the slope was 0.061, the t value, as already noted, 3.64.)

In contrast, no significant positive relation was demonstrable between average serum triglyceride values on entry and any of the four end points, by either univariate or multivariate analysis (Fig. 3). In fact, for one of the four end points—incidence of major coronary events—the multivariate adjusted slope had a fairly large negative value (b = −0.49, t = −2.66); that is, the higher the level of baseline serum triglycerides, the smaller was the risk of a major coronary event during the 5 years of follow-up.

Bivariate analyses yielded results consistent with these findings. Thus, linear regression analysis of the two variables simultaneously indicated a significant relation between serum cholesterol and each of the four end points, but no significant triglyceride effect. Inclusion of an interaction term in the model showed no significant interaction effect. The regression lines derived from these analyses are plotted in Figures 4 and 5. Also shown in these figures are the observed event rates for the nine groups identified by classification of the men based simultaneously on low, medium and high cholesterol and low, medium and high triglyceride levels. Figure 4 shows the groups arranged to demonstrate the cholesterol effect within the triglyceride subgroups. Figure 5 presents the same groups arranged to show the triglyceride effect. The slopes of the regression lines are not identical because of the minor interaction effects; that is, the slope of the regression line for cholesterol depends slightly upon the triglyceride level, and vice versa.

Among the nine groups presented in this analysis, the highest 5 year mortality rate from all causes (27.9 percent) was for the group with high cholesterol and low triglyceride levels. The rate for the group with high cholesterol and high triglyceride levels was 21.3 percent.

The various analyses described were repeated after a logarithmic transformation was applied to the triglyceride values to take account of the skewness of the distribution. Generally similar results were obtained. Further, adding the quadratic terms for the cholesterol and triglyceride effects led to only very minor increases in the multiple regression coefficients, indicating that these additional terms did not increase the power of the regression equations to estimate long-term risk after myocardial infarction.

Discussion

Serum cholesterol and long-term prognosis: Our data demonstrate a clear-cut significant relation between baseline serum cholesterol level and long-term prognosis for men recovered from myocardial infarction. This result emerged from analyses using the mean of three baseline serum cholesterol values for each man. It was found for all four end points evaluated—death from all causes, coronary mortality, sudden coronary death and incidence of major coronary events (nonfatal myocardial infarction plus coronary death). It was shown to persist independently and significantly after statistical adjustment for 39 other variables (demographic, electrocardiographic, roentgenographic, medical historical, biochemical, therapeutic) possibly related to long-term prognosis after myocardial infarction.

These findings strongly indicate that serum cholesterol not only is significantly and independently related to risk of a *first* major coronary event—a phenomenon repeatedly demonstrated both retrospectively and prospectively[12–38]—but also has significance for long-term prognosis when measured after recovery from one or more myocardial infarctions, although the force of the relation (relative risk) is conspicuously less. In this latter respect, our data are consistent with results of one other published study, from Oslo, Norway,[42] as well as with data presented (but not yet published) from Rochester, Minnesota.[47] They are at variance with the negative results reported by two other studies, from Toronto, Canada and New York, New York.[39–41] The reasons for the discrepancy are not immediately apparent. They may reflect differences in numbers of patients studied (2,789 placebo patients in the Coronary Drug Project versus 120 and 470 in the Toronto and New York studies); differences in average time after myocardial infarction on entry into the study (36 months in the Coronary Drug Project, 6 months in the New York study and unreported in the Toronto study, but apparently about 4 years on the basis of the data presented); differences in patient characteristics; and differences in control for other possible confounding variables (examined in detail for 39 other variables in the Coronary Drug Project, but not reported in the two other studies).

Serum triglycerides and long-term prognosis: Our data demonstrated a relation of serum cholesterol to 5 year incidence of events after myocardial infarction irrespective of baseline fasting serum triglyceride level, that is, for men with low, medium and high serum triglyceride levels. In contrast, we found no relation between serum triglycerides and incidence of events after infarction. These negative results consistently emerged

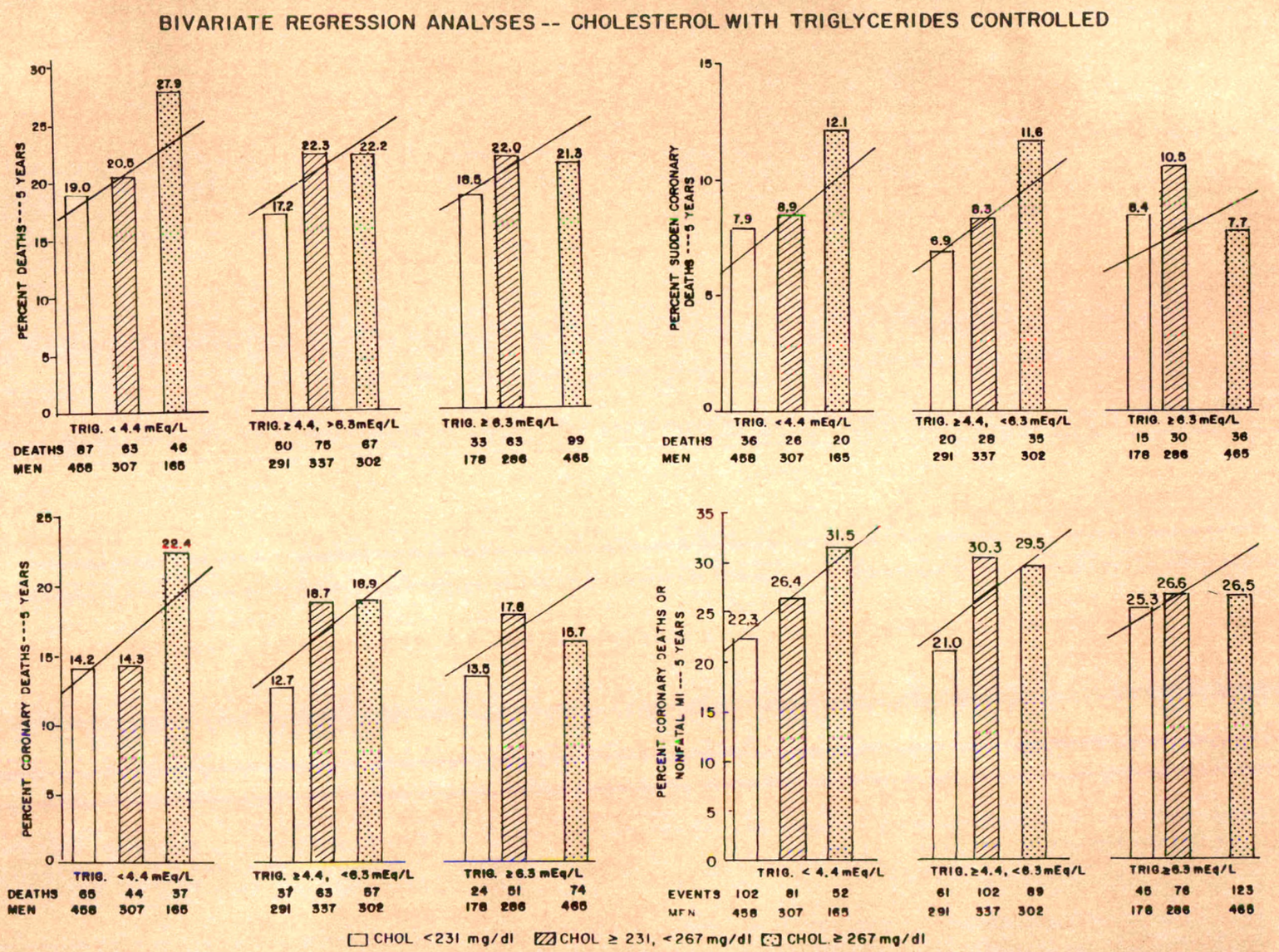

FIGURE 4. Analyses, with baseline serum fasting triglyceride (TRIG.) levels controlled, of relations between baseline serum cholesterol (CHOL.) levels and 5 year rates for four stipulated end points for the 2,789 men studied. The slopes in each graph are obtained by inserting the mean value of the triglyceride levels for each of the three subgroups (3.4, 5.2 and 10.1 mEq/liter, respectively) into the regression equation including cholesterol, triglycerides and their interaction. L = liter; MI = myocardial infarction.

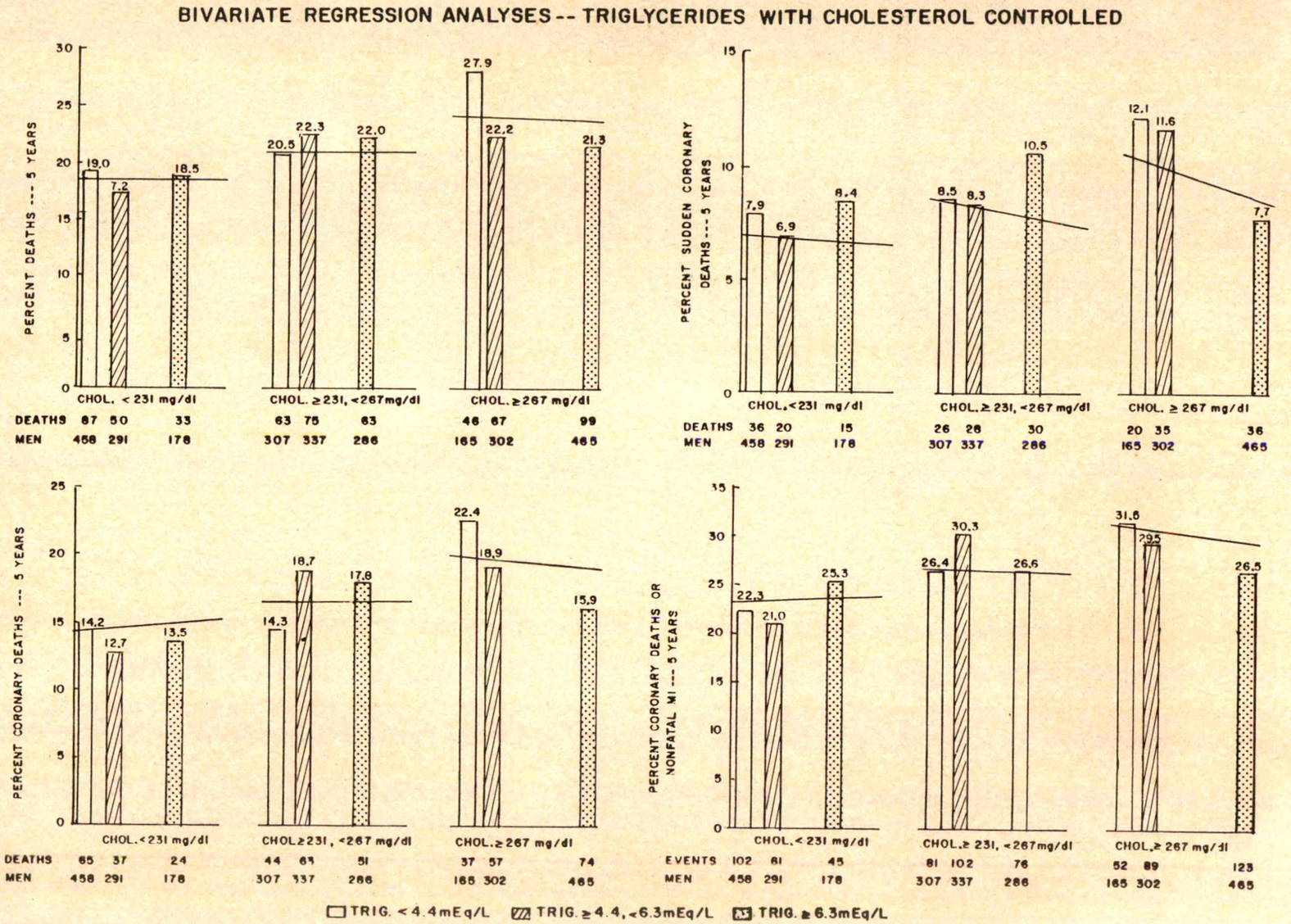

FIGURE 5. Analyses, with baseline serum cholesterol (CHOL.) levels controlled, of relations between baseline fasting serum triglyceride (TRIG.) levels and 5 year rates for four stipulated end points for the 2,789 men studied. The slopes in each graph are obtained by inserting the mean value of the cholesterol levels for each of the three subgroups (206.2, 248.2, 302.6 mg/dl, respectively) into the regression equation including cholesterol, triglycerides and their interaction. L = liter; MI = myocardial infarction.

for all four end points, in univariate, bivariate (triglycerides and cholesterol) and multivariate (triglycerides plus 38 or 39 other baseline characteristics) analyses. They strongly indicate that fasting serum triglycerides have no relation to long-term prognosis after myocardial infarction or, possibly, an inverse relation (that is, at any level of serum cholesterol, the lower the serum triglyceride level, the *worse* the prognosis, particularly at higher levels of serum cholesterol). This finding may indeed "make sense" biologically because there is published evidence[48–52] that cholesterol borne by smaller low density lipoprotein (LDL) may be more atherogenic, milligram for milligram, than cholesterol in very low density lipoprotein (VLDL). These theoretical considerations apart, the Coronary Drug Project data lend no support to the hypothesis that serum triglycerides are prognostically important—at least not after recovery from one or more definite myocardial infarctions.

The Coronary Drug Project Research Group is unaware of data from any other study on serum triglycerides and long-term prognosis after myocardial infarction. To our knowledge, the only reports available relate to risk of *first*—rather than *recurrent*—coronary events. In univariate analyses, serum triglycerides (and their main lipoprotein carriers, VLDL) do in some—but not most—studies relate positively to risk of a first coronary episode. Moreover, multivariate analyses generally indicate that this association is *not* independent of the relation of serum cholesterol (and its main lipoprotein carrier, LDL) to risk of a first coronary event.[16,17,22–24,28,29,53–56] One report[30] from Stockholm, Sweden has concluded that serum triglycerides are related to risk of first coronary events independent of and additive to serum cholesterol. However, the supporting statistics are not convincing because they entailed dichotomization of the data for the two variables on the basis of arbitrary cut points and included no regression analysis. A recent report[32] from Finland has presented data indicating a contribution of fasting triglycerides to risk of a first coronary event independent of serum cholesterol. Whatever the case in regard to first events, the Coronary Drug Project 5 year data clearly indicate *no* positive relation between fasting serum triglycerides and risk of recurrent coronary events or death for middle-aged American men after myocardial infarction.

Therapeutic implications: A further comment is in order on the quantitative aspects of the positive relation between serum cholesterol and coronary risk after myocardial infarction and their implications for a possible therapeutic benefit by reducing serum cholesterol after myocardial infarction, and for testing this possibility in randomized controlled trials. As indicated in Figure 2, the value of the slope (b) of the relation between cholesterol and mortality from all causes was 0.05, both unadjusted and adjusted for 38 other factors. For the entire cohort of 2,789 men in the placebo group, mean serum cholesterol was about 250 mg/dl and the 5 year mortality rate was 20.9 percent. Currently, a reasonable possibility for overall reduction of serum cholesterol by nutritional or pharmacologic means, or both, is in the range 10 to 20 percent, that is, a reduction of 25 to 50 mg/dl on the average for men like those in the Coronary Drug Project.[3,5,12,13,19,48,49,57–62] On the basis of a value of 0.05 for the slope of the cholesterol-mortality relation, a 10 percent or 25 mg/dl decrease in serum cholesterol could hypothetically lead to a decrease in mortality of 1.25 percentage points, or a 6 percent decrease in mortality (1.25/20.9). A reduction in serum cholesterol by 20 percent or 50 mg/dl could hypothetically produce twice the decrease in mortality, or 2.50 percentage points, equal to a decline in the death rate of 12 percent (2.50/20.9). Calculations for the three other end points yield similar results. These are far less proportionately—that is, relatively—than those estimated as being theoretically possible by similar lowering of serum cholesterol for persons free of clinical coronary heart disease.[13,61,63,64] Thus the Coronary Drug Project findings highlight the need for a strategy focused on primary prevention to control the current epidemic of coronary heart disease.[12,13,28,64] Nevertheless, a 6 to 12 percent reduction in 5 year mortality for patients after myocardial infarction would not be negligible, in view of the high absolute risk, that is, about 20 percent in 5 years. Thus, a reduction of 6 percent in this mortality rate would save 12 lives among 1,000 such men per 5 years, and a reduction of 12 percent would save 24 lives. This absolute saving in lives per 1,000 is by no means inferior to that theoretically achievable by similar cholesterol reduction before myocardial infarction when the absolute risk is considerably lower. The import of this possibility is clear when it is recalled that in the United States young adult and middle-aged persons with clinically manifest coronary heart disease number in the millions.

Whether such hypothetical reductions in mortality for patients after myocardial infarction are attainable by safe means to lower serum cholesterol (for example, calorie-controlled diets low in saturated fat and cholesterol), has not been clarified by any randomized controlled experiment. Moreover, at present no plans are under way—to the best of our knowledge—to mount such a further large-scale trial of secondary prevention through reduction of serum cholesterol levels, by diet or drugs, or both. Therefore, physicians will have to advise their patients with coronary heart disease on the basis of the best judgment of the available evidence, short of definitive data from randomized controlled trials. The Coronary Drug Project data presented here support the inference that safe nutritional means to reduce serum cholesterol may be useful after myocardial infarction as part of the total therapeutic regimen to improve long-term prognosis.

Appendix

The key bodies of the Coronary Drug Project and their senior staff members are as follows:

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References

1. Coronary Drug Project Research Group: The Coronary Drug Project: design, methods and baseline results. Circulation 47: Suppl I: I1–I50, 1973
2. Coronary Drug Project Research Group: The Coronary Drug Project: initial findings leading to modification of its research protocol. JAMA 214:1303–1313, 1970
3. Coronary Drug Project Research Group: The Coronary Drug Project: findings leading to further modifications of its protocol with respect to dextrothyroxine. JAMA 220:996–1008, 1972
4. Coronary Drug Project Research Group: The Coronary Drug Project: findings leading to discontinuation of the 2.5 mg/day estrogen group. JAMA 226:652–657, 1973
5. Coronary Drug Project Research Group: The Coronary Drug Project: clofibrate and niacin in coronary heart disease. JAMA 231: 360–381, 1975
6. Coronary Drug Project Research Group: Factors influencing long-term prognosis after recovery from myocardial infarction: 3-year findings of the Coronary Drug Project. J Chronic Dis 27: 267–285, 1974
7. Coronary Drug Project Research Group: The prognostic importance of the electrocardiogram after myocardial infarction: experience in the Coronary Drug Project. Ann Intern Med 77:677–689, 1972
8. Coronary Drug Project Research Group: Prognostic importance of premature beats following myocardial infarction. Experience in the Coronary Drug Project. JAMA 223:1116–1124, 1973
9. Coronary Drug Project Research Group: Left ventricular hypertrophy patterns and prognosis: experience postinfarction in the Coronary Drug Project. Circulation 49:863–869, 1974
10. Coronary Drug Project Research Group: Serum uric acid: its association with other risk factors and with mortality in coronary heart disease. J Chronic Dis 29:557–569, 1976
11. Coronary Drug Project Research Group: The prognostic importance of plasma glucose levels and of the use of oral hypoglycemic drugs after myocardial infarction in men. Diabetes 26:453–465, 1977
12. **Stamler J:** Lectures on Preventive Cardiology. New York, Grune & Stratton, 1967
13. Inter-Society Commission for Heart Disease Resources: Atherosclerosis Study Group and Epidemiology Study Group: primary prevention of the atherosclerotic diseases. Circulation 42:A55-A95, 1970
14. **McGee D, Gordon T:** The Framingham Study—An Epidemiological Investigation of Cardiovascular Disease. Section 31. The Results of the Framingham Study Applied to Four Other U.S.-Based Epidemiologic Studies of Cardiovascular Disease. US Department of Health, Education, and Welfare, DHEW Publication no. (NIH) 76-1083, Washington, DC, April 1976
15. Pooling Project Research Group: Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final report of the pooling project. J Chronic Dis, in press
16. **Rosenman RH, Brand RJ, Jenkins D, et al:** Coronary heart disease in the Western Collaborative Group Study. Final follow-up experience of 8½ years. JAMA 233:872–877, 1975
17. **Rosenman RH, Brand RJ, Sholtz RI, et al:** Multivariate prediction of coronary heart disease during 8.5 year follow-up in the Western Collaborative Group Study. Am J Cardiol 37:903–910, 1976
18. **Tyroler HA, Heyden S, Bartel A, et al:** Blood pressure and cholesterol as coronary heart disease risk factors. Arch Intern Med 128:907–914, 1971
19. **Kleinbaum DG, Kupper LL, Cassel JC, et al:** Multivariate analysis of risk of coronary heart disease in Evans County, Georgia. Arch Intern Med 128:943–948, 1971
20. **Friedman GD, Klatsky AL, Siegelaub AB, et al:** Kaiser-Permanente

epidemiologic study of myocardial infarction. Am J Epidemiol 99:101–116, 1974
21. **Stamler J, Schoenberger JA, Shekelle RB, et al:** Relationship of glucose tolerance to 5-year mortality from coronary heart disease: findings of the Chicago Heart Association detection project in industry in employed middle-aged Chicago men, in preparation
22. **Robertson TL, Kato H, Gordon T, et al:** Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California. Coronary heart disease risk factors in Japan and Hawaii. Am J Cardiol 39:244–249, 1977
23. **Gordon T, Garcia-Palmieri MR, Kagan A, et al:** Differences in coronary heart disease in Framingham, Honolulu and Puerto Rico. J Chronic Dis 27:329–344, 1974
24. **Kagan A, Gordon T, Rhoads GG, et al:** Some factors related to coronary heart disease incidence in Honolulu Japanese men: The Honolulu Heart Study. Int J Epidemiol 4:271–279, 1975
25. **Morris JN, Marr JW, Clayton DG:** Diet and heart: a postscript. Br Med J 2:1307–1314, 1977
26. **Rose G:** The Basic Principles of Multifactorial Prediction and Control. Proceedings of a Symposium, "From Epidemiology to Prevention," sponsored by the World Health Organization and the European Society of Cardiology. Megéve, Switzerland, Merck, Sharp and Dohme, 1974, p 107–110
27. **Rose G, Reid DD, Hamilton PJS, et al:** Myocardial ischaemia, risk factors and death from coronary heart-disease. Lancet 1:105–109, 1977
28. **Wilhelmsen L, Wedel H, Tibblin G:** Multivariate analysis of risk factors for coronary heart disease. Circulation 48:950–958, 1973
29. **Tibblin G, Wilhelmsen L, Werkö L:** Risk factors for myocardial infarction and death due to ischemic heart disease and other causes. Am J Cardiol 35:514–522, 1975
30. **Carlson LA, Böttiger LE:** Ischaemic heart-disease in relation to fasting values of plasma triglycerides and cholesterol. Lancet 1: 865–868, 1972
31. **Pyörälä K, Heikkilä J, Luomanmäki K:** Sydaninfarkti ja sen hoito arvioitavana. Duodecim 93:79–81, 1977
32. **Pelkonen R, Nikkilä EA, Koskinen S, et al:** Association of serum lipids and obesity with cardiovascular mortality. Br Med J 2: 1185–1187, 1977
33. **Menotti A, Capocaccia R, Conti S, et al:** Identifying subsets of major risk factors in multivariate estimation of coronary risk. J Chronic Dis 30:557–565, 1977
34. **Kozarevic D, Pirc B, Racic Z, et al:** The Yugoslavia cardiovascular disease study. II. Factors in the incidence of coronary heart disease. Am J Epidemiol 104:133–140, 1976
35. **Ducimetiere P, Warnet JM, Richard JL:** Raised serum alpha-2 globulins as an independent risk factor of coronary heart disease. J Chronic Dis 29:423–429, 1976
36. **Medalie JH, Kahn HA, Neufeld HN, et al:** Five-year myocardial infarction incidence. II. Association of single variables to age and birthplace. J Chronic Dis 26:329–349, 1973
37. **Goldbourt U, Medalie JH, Neufeld HN:** Clinical myocardial infarction over a 5-year period. III. A multivariate analysis of incidence, the Israel ischemic heart disease study. J Chronic Dis 28:217–237, 1975
38. **Cullen KJ:** Mass health examinations in the Busselton population, 1966 to 1970. Med J Aust 2:714–718, 1972
39. **Little JA, Shanoff HM, Roe RD, et al:** Studies of male survivors of myocardial infarction. IV. Serum lipids and five-year survival. Circulation 31:854–862, 1965
40. **Weinblatt E, Shapiro S, Frank CW, et al:** Prognosis of men after first myocardial infarction: mortality and first recurrence in relation to selected parameters. Am J Public Health 58:1329–1347, 1968
41. **Frank CW, Weinblatt E, Shapiro S:** Angina pectoris in men: prognostic significance of selected medical factors. Circulation 47:509–517, 1973
42. **Leren P:** The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. A controlled clinical trial. Acta Med Scand Suppl 466:1–90, 1966
43. Criteria Committee of the New York Heart Association: Diseases of the Heart and Blood Vessels: Nomenclature and Criteria for Diagnosis, sixth edition. Boston, Little, Brown, 1964
44. **Abell LL, Levy BB, Brodie BB, et al:** Simplified method for the estimation of total cholesterol in serum and demonstration of its specificity. J Biol Chem 195:357–366, 1952
45. **Van Handel E, Zilversmit DB:** Micromethod for the direct determination of serum triglycerides. J Lab Clin Med 50:152–157, 1957
46. **Lofland HB Jr:** Semiautomated procedure for the determination of triglycerides in serum. Anal Biochem 9:393–400, 1964
47. **Oxman HA, Connolly DC, Nobrega, FT, et al:** Identification of the patients at higher risk for sudden death within five years following their first myocardial infarction. Presented at the Conference on Cardiovascular Disease Epidemiology, Council on Epidemiology, American Heart Association, New Orleans, LA, March 12–13, 1973
48. Atherosclerosis, Second International Symposium (Jones RJ, ed). New York, Springer-Verlag, 1970
49. Atherosclerosis III (Schettler G, Weizel A, ed). Berlin, New York, Springer-Verlag, 1974
50. **Stamler J, Berkson DM, Lindberg HA:** Risk factors: their role in the etiology and pathogenesis of the atherosclerotic diseases. In, The Pathogenesis of Atherosclerosis (Wissler RW, Geer JC, ed). Baltimore, Williams & Wilkins, 1972, p 41–119
51. Atherosclerosis Reviews, I (Paoletti R, Gotto A, ed). New York, Raven Press, 1976
52. Atherosclerosis Reviews, II (Paoletti R, Gotto A, ed). New York, Raven Press, 1977
53. **Gofman JW, Andrus EC, et al:** Evaluation of serum lipoprotein and cholesterol measurements as predictors of clinical complications of atherosclerosis. Report of a cooperative study of lipoproteins and atherosclerosis. Circulation 14:691–741, 1956
54. **Gofman JW, Young W, Tandy R:** Ischemic heart disease, atherosclerosis, and longevity. Circulation 34:679–697, 1966
55. **Kannel WB, Castelli WP, Gordon T, et al:** Serum cholesterol, lipoproteins, and the risk of coronary heart disease: The Framingham Study. Ann Intern Med 74:1–12, 1971
56. **Gordon T, Castelli WP, Hjortland MC, et al:** Predicting coronary heart disease in middle-aged and older persons. JAMA 238: 497–499, 1977
57. **Dayton S, Pearce ML, Hashimoto S, et al:** A controlled clinical trial of a diet high in unsaturated fat. Preventing complications of atherosclerosis. Circulation 39, 40:Suppl II: II1–II63, 1969
58. **Turpeinen O, Miettinen M, Karvonen MJ, et al:** Dietary prevention of coronary heart disease: long-term experiment. I. Observations on male subjects. Am J Clin Nutr 21:255–276, 1968
59. **Miettinen M, Turpeinen O, Karvonen MJ, et al:** Effect of cholesterol-lowering diet on mortality from coronary heart disease and other causes. A twelve-year clinical trial in men and women. Lancet 2:835–838, 1972
60. **Rinzler SH:** Primary prevention of coronary heart disease by diet. Bull NY Acad Med 44:936–949, 1968
61. National Diet-Heart Study Research Group: The National Diet-Heart Study Final Report. Circulation 37:Suppl I: I-1–I-48, 1968
62. **Farinaro E, Stamler J, Upton M, et al:** Plasma glucose levels: long-term effect of diet in the Chicago Coronary Prevention Evaluation Program. Ann Intern Med 86:147–154, 1977
63. **Stamler J:** The challenges and possibilities for prevention in mass community efforts to control the major coronary risk factors. In, Preventive Cardiology (Tibblin G, Keys A, Werkö L, ed). Stockholm, Almqvist & Wiksell, 1972, p 13–17
64. **Stamler J:** Introduction. In, Risk Factors in Coronary Artery Disease (McIntosh HD, ed). Baylor College of Medicine Cardiology Series, Vol 1, Part 3. Northfield, IL, Medical Communications, 1978

MSD ANNOUNCES

NEW

TABLETS

Aldoril® D30

D, the Roman numeral for 500, stands for 500 mg ALDOMET® (Methyldopa, MSD) and 30 for 30 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

NEW

TABLETS

Aldoril® D50

D, the Roman numeral for 500, stands for 500 mg ALDOMET® (Methyldopa, MSD) and 50 for 50 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

MSD
MERCK SHARP & DOHME

For a brief summary of prescribing information, please see last page of this advertisement.

Practical antihypertensive therapy

for a broad range of active patients*

ALDORIL®, containing ALDOMET® (Methyldopa, MSD) and HydroDIURIL® (Hydrochlorothiazide, MSD)—two highly effective complementary agents—offers:

b.i.d. convenience for many patients

b.i.d. doses can be used for many patients.

more economical therapy

ALDORIL may offer more economical therapy than individual prescriptions for both HydroDIURIL and ALDOMET.

daily activities usually not affected

Exercise hypotension and diurnal blood pressure variations rarely occur. There is less frequent symptomatic postural hypotension than with many other antihypertensive agents.

no overshoot

Since both components of ALDORIL have a relatively short duration of action, withdrawal is followed by a return of hypertension usually within 48 hours. This is not complicated by an overshoot of blood pressure.

favorable cardiac profile

Neither component of ALDORIL usually has any direct effect on cardiac function in long-term therapy—cardiac output is usually maintained.

ALDORIL is contraindicated in active hepatic disease; anuria; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs; if previous methyldopa therapy has been associated with liver disorders.

In patients with renal disease, thiazides may precipitate azotemia. Use with caution in patients with severe renal disease or impaired hepatic function.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, see the brief summary of prescribing information.

NEW

TABLETS

Aldoril® D30

containing 500 mg ALDOMET® (Methyldopa, MSD) and 30 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

NEW

TABLETS

Aldoril® D50

containing 500 mg ALDOMET® (Methyldopa, MSD) and 50 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

ALSO AVAILABLE

TABLETS

ALDORIL®-25 containing 250 mg ALDOMET® (Methyldopa, MSD) and 25 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

TABLETS

ALDORIL®-15 containing 250 mg ALDOMET® (Methyldopa, MSD) and 15 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

*As a fixed combination, ALDORIL is not indicated for initial therapy since hypertension requires therapy titrated to the individual patient's needs. If an available strength of ALDORIL meets the patient's titrated needs, the combination drug may be more convenient in patient management. Therapy should be reevaluated as necessary.

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For a brief summary of prescribing information, please see following page.

Antihypertensive TABLETS

New ALDORIL® D50
methyldopa 500 mg and hydrochlorothiazide 50 mg

Antihypertensive TABLETS

New ALDORIL® D30
methyldopa 500 mg and hydrochlorothiazide 30 mg

Antihypertensive TABLETS

ALDORIL®-25
methyldopa 250 mg and hydrochlorothiazide 25 mg

Antihypertensive TABLETS

ALDORIL®-15
methyldopa 250 mg and hydrochlorothiazide 15 mg

WARNING

This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be re-evaluated as conditions in each patient warrant.

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see **Warnings**); anuria; routine use in an otherwise healthy pregnant woman with or without mild edema; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs.

Warnings: METHYLDOPA—**It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.**

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within the first three weeks of therapy, sometimes with eosinophilia or abnormalities in one or more liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually within the first two to three months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, reversible reduction of white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Follow patients carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

HYDROCHLOROTHIAZIDE—Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity; read circulars for lithium preparations before use of such concomitant therapy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks.

Methyldopa and thiazides cross the placental barrier and appear in cord blood.

No unusual adverse reactions have been reported in association with the use of methyldopa during pregnancy. Although no obvious teratogenic effects have been reported, the possibility of fetal injury cannot be excluded.

The hazards of thiazides crossing the placental barrier include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in adults. Methyldopa and thiazides appear in breast milk. Patients taking ALDORIL should not nurse.

Precautions: METHYLDOPA—Should be used with caution in patients with history of previous liver disease or dysfunction (see **Warnings**). May interfere with measurement of urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.. Involuntary choreoathetotic movements have been observed in patients with severe bilateral cerebrovascular disease. If such movements occur, stop the drug. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

HYDROCHLOROTHIAZIDE—Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroids or ACTH, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: METHYLDOPA—*Central nervous system:* Sedation, headache, asthenia or weakness; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression. *Cardiovascular:* Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.) *Gastrointestinal:* Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. *Hepatic:* Abnormal liver function tests, jaundice, liver disorders. *Hematologic:* Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells and rheumatoid factor. *Allergic:* Drug-related fever, lupus-like syndrome, myocarditis. *Other:* Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

HYDROCHLOROTHIAZIDE—*Gastrointestinal system:* Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis. *Central nervous system:* Dizziness, vertigo, paresthesias, headache, xanthopsia. *Hematologic:* Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. *Cardiovascular:* Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics). *Hypersensitivity:* Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions. *Other:* Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: Tolerance may occur, usually between the second and third month of therapy. Increasing dosage of either component separately or together frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets ALDORIL®-15, containing 250 mg methyldopa and 15 mg hydrochlorothiazide, bottles of 100 and 1000; Tablets ALDORIL®-25, containing 250 mg methyldopa and 25 mg hydrochlorothiazide, bottles of 100 and 1000; Tablets ALDORIL® D30, containing 500 mg methyldopa and 30 mg hydrochlorothiazide, bottles of 100; Tablets ALDORIL® D50, containing 500 mg methyldopa and 50 mg hydrochlorothiazide, bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486. J7AR08 (021)

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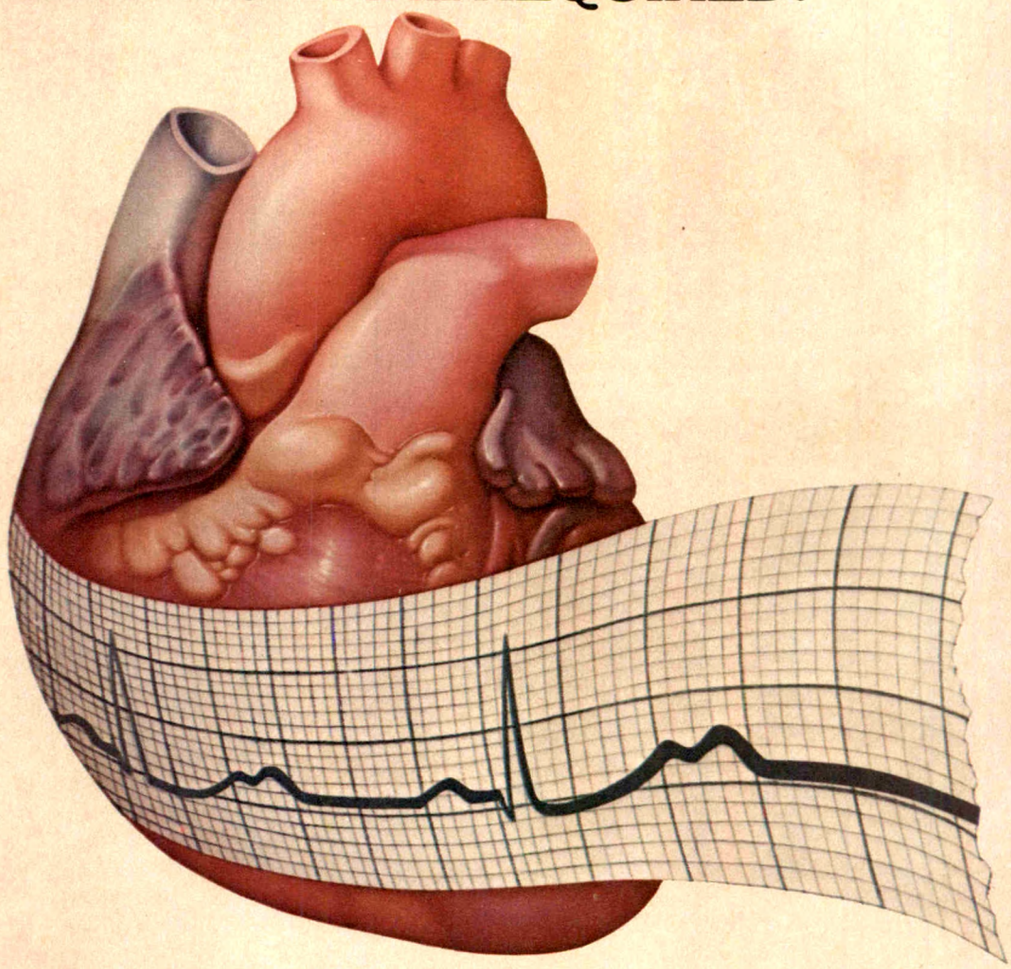
WHEN THERAPEUTIC DOSES OF POTASSIUM ARE REQUIRED:



CONVENIENT AND ECONOMICAL

KAON-CL 20%®

(potassium chloride) LIQUID

40 mEq per 15 ml

Indications: KAON-CL 20% is indicated for the treatment of potassium depletion in patients with hypokalemia and metabolic alkalosis, and for the treatment of digitalis intoxication. During therapy serum potassium levels should be monitored and the dosage titrated to achieve the desired clinical and laboratory effects. KAON-CL 20% is also indicated for the prevention of potassium depletion when the dietary intake of potassium is inadequate for this purpose. The prophylactic administration of potassium ion may be indicated in patients receiving digitalis and diuretics for the treatment of congestive heart failure, hepatic cirrhosis with ascites, patients with hypertension on long-term diuretic therapy, hyperaldosteronism states with normal renal function, the nephrotic syndrome, and certain diarrheal states.

Contraindications: In patients with hyperkalemia, chronic renal failure, systemic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Warnings: Do not administer full strength. KAON-CL 20% will cause gastrointestinal irritation if administered undiluted.

In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: Nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effect is hyperkalemia (see Contraindications, Warnings and Overdosage).

Overdosage: If excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes. Late manifestations include muscle paralysis and cardiovascular collapse from cardiac arrest.

How Supplied: Pints, gallons and 4 fl. oz.

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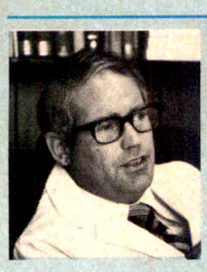
Inner-View No. 2

A continuing educational series in Nuclear Cardiology



The interview excerpted here was conducted with Glen W. Hamilton, M.D., Chief, Nuclear Medicine Section, Veteran's Administration Hospital, Seattle, Washington. Dr. Hamilton is also an Associate Professor of Medicine, University of Washington School of Medicine.

Q. Of the nuclear cardiology studies available in clinical practice today, which are the most difficult to interpret?

A. Thallium images are probably the most difficult to interpret, and pyrophosphate are probably the next. In about 60% of all abnormal studies, the abnormality is quite obvious. The remaining 40% are quite difficult to read. As the physician gains experience, he will be able to read about half of those with confidence, but about 20% of all thallium studies remain difficult to interpret. Experienced observers will have legitimate disagreement as to whether a given study is normal or abnormal.

Q. Which of these tests are generally the best in the assessment of left ventricular function? Is this also the best study for assessing wall motion?

A. The multiple gated blood pool study yields the greatest clinical information compared to the difficulty of performing the test and, therefore, is the one we use in our clinical practice when we wish to assess a patient's ventricular function. The best study for assessing wall motion is probably the multiple gated study. It is not perfect, in that the right ventricle and the left ventricle overlap in all but the LAO view... but for most laboratories it is the most practical way to assess wall motion.

Q. What studies would you recommend to a nuclear physician or cardiologist beginning nuclear cardiology in a community hospital?

A. I would recommend two studies: multiple gated blood pool studies, and thallium imaging. The ventricular function measurements obtained from multiple gated studies are useful not only in patients who have suspected coronary disease, but also in a wide variety of other patients, such as people with lung disease, older patients who have undetected ventricular dysfunction, or presurgical patients. Clearly, this is going to be the largest volume study, and that's the place where they should start. After doing resting ventricular function studies, they should progress to thallium imaging. Six months from now, there should be enough data available on rest/exercise ventricular function studies using multiple gated imaging to indicate whether this technique is of general usefulness.

Q. Which studies are most difficult to perform?

A. Pyrophosphate studies are obviously the simplest to perform. The multiple gated blood pool study is performed quite simply. However, the equipment required is not present in every laboratory at the present time. Thallium, being a less ideal isotope, is probably the most difficult study, in terms of the technique required to achieve good diagnostic results.

Q. What may be the single most important use of these nuclear cardiology studies in five years?

A. First, I'm confident we will be noninvasively measuring ventricular function in a wide range of patients with various disease states — coronary artery disease, cardiomyopathy, chronic lung disease, valvular heart disease and many others. We will be able to follow these patients, correctly select the optimal time for surgical intervention, and alter medical therapy so that treatment is optimal. There's no question that this will happen. Secondly, if these tests turn out to be quite sensitive for the detection of coronary artery disease in its early presymptomatic stages, it may be possible to alter that disease by various interventions. This could become a very important national endeavor which could have far-ranging effects on health in this country.

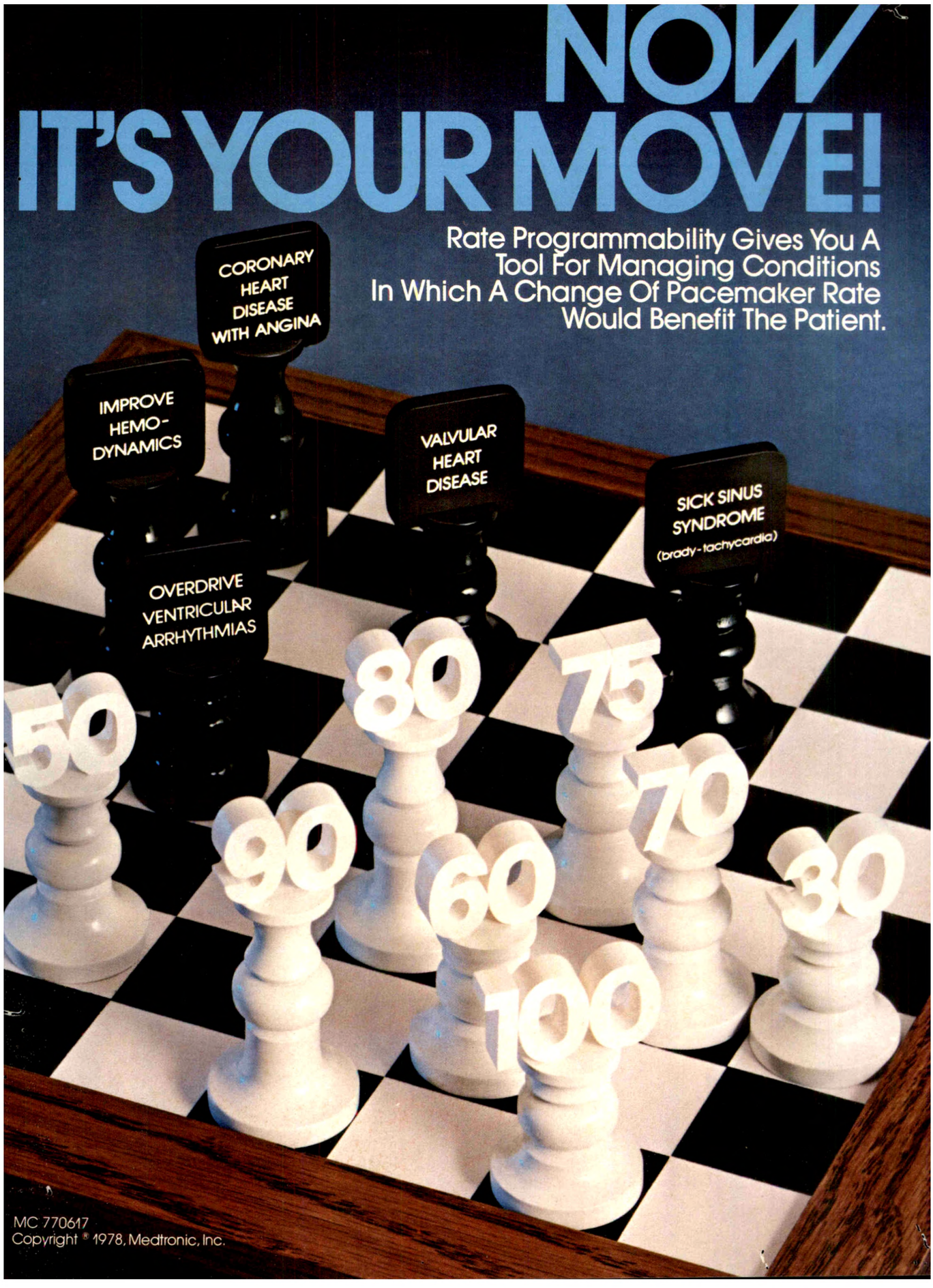
Q. How widespread do you see these techniques becoming?

A. The need for studies of ventricular function will be comparable to the need for lung or bone scans. I really expect that most existing nuclear medicine laboratories, and, generally any hospital of two or three hundred beds, will be able to perform ventricular function studies within the next several years.

For the complete transcript of this interview with Dr. Hamilton, write Inner-View, General Electric Company, Medical Systems Division, P.O. Box 414 (Mail Code W-504), Milwaukee, WI 53201.

General Electric Medical Systems, Milwaukee, Toronto, Madrid.

GENERAL ELECTRIC


NOW
IT'S YOUR MOVE!
Rate Programmability Gives You A Tool For Managing Conditions In Which A Change Of Pacemaker Rate Would Benefit The Patient.
CORONARY HEART DISEASE WITH ANGINA
IMPROVE HEMO-DYNAMICS
VALVULAR HEART DISEASE
SICK SINUS SYNDROME (brady-tachycardia)
OVERDRIVE VENTRICULAR ARRHYTHMIAS
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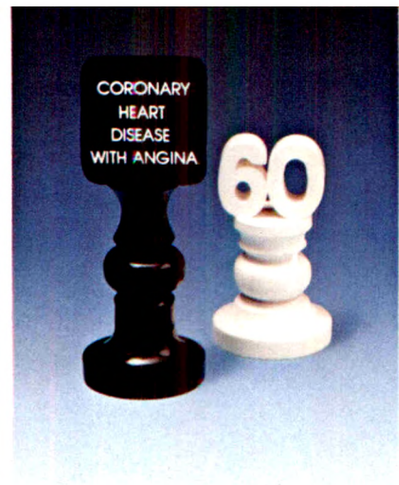
THERE ARE AT LEAST FIVE APPLICATIONS IN WHICH HAVING THE FLEXIBILITY OF CHANGING PACED RATE CAN PROVIDE MORE VERSATILITY IN PATIENT MANAGEMENT.

These applications are:

1. Sick Sinus Syndrome (brady-tachycardia).
2. Coronary heart disease with angina pectoris.
3. Valvular heart disease.
4. To overdrive ventricular arrhythmias.
5. To improve hemodynamics.

In each of these, having the ability to change the pacing rate can preserve, maintain or improve the quality of life for pacemaker patients. Furthermore, because of the potential longevity of lithium pacemakers, the physician can take advantage of the greater flexibility provided by rate programmability to respond to the patient's changing medical condition during the pulse generator service life.

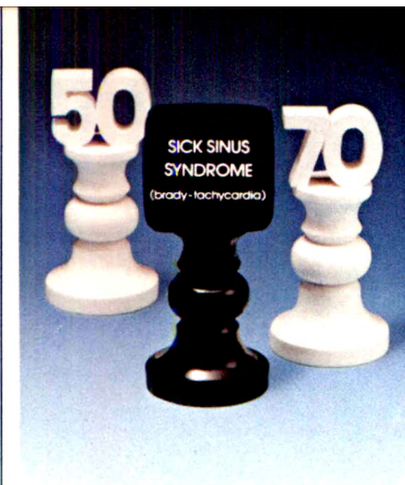


USING RATE PROGRAMMABLE PACEMAKERS IN CORONARY HEART DISEASE WITH ANGINA PECTORIS

Not infrequently, the patient in whom pacing is indicated presents with coronary artery disease and angina pectoris.

Angina may be occurring as a consequence of heart rate exceeding the ability of the coronary artery network to provide adequate circulation to myocardial tissue. Since heart tissues receive nutrients during diastole, it is felt that a slower heart rate and a corresponding longer diastolic period may provide enhanced opportunity for energy and oxygen transfer to myocardial tissue.

In any event, a rate programmable pacemaker permits evaluation for clinical symptoms at various rates and can permit selection of a pacing rate which is not likely to provoke angina, while providing the patient with adequate exertional status.



THE APPLICATION OF RATE PROGRAMMING IN BRADY-TACHYCARDIA (SICK SINUS SYNDROME).

After the physician has determined that artificial heart pacemaking is the treatment of choice for the patient with brady-tachycardia, he may contemplate application of a rate-programmable pacemaker to treat this disease.

Because brady-tachycardia may be a progressive disease, it is often appropriate to implant a rate-programmable pacemaker.

For example, in the early stages of the disorder, the patient may require pacing for just a few seconds a month when the intrinsic rate drops below a rate which the physician has determined provides adequate cardiac output. In such a situation, the pacemaker is set at a low rate (i.e., 50 or 60 ppm) to provide an underlying safe rhythm, but which allows the patient the benefit of his normal atrial ventricular contraction sequence.

Sick sinus syndrome at times is a progressive disorder which may result in a slowing of the patient's normal sinus rhythm. This slowing may be gradual or sudden. Frequently, it is accompanied by a tendency towards a more unreliable rhythm. The patient, thus, increases his or her reliance on the pacemaker for adequate heart rate.

Rate programming at increasingly higher rates may help maintain cardiac output at adequate levels when the pacemaker is needed to provide the dominant rhythm. An increase in pacemaker rate may also be needed to prevent the emergence of a less suitable tachyarrhythmia.

THE APPLICATION OF RATE PROGRAMMABLE PULSE GENERATORS IN VALVULAR HEART DISEASE

The clinical course for pacemaker patients with valvular heart disease is complex and unpredictable.

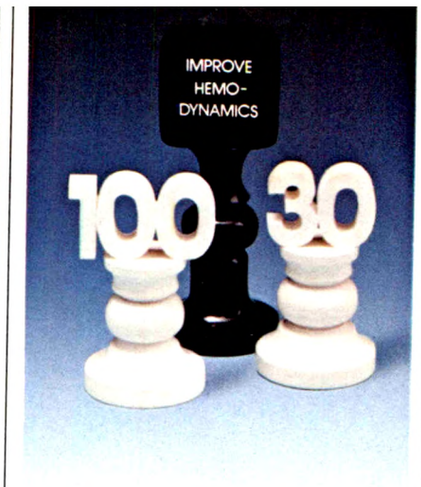
Many of these patients require a pacemaker prior to operation for their valve lesion.

The patient with aortic stenosis may need to have his rate adjusted to a slow level to allow for complete emptying of the ventricle. Too fast a rate increases ventricular pressure and restricts the flow of blood from the coronary arteries to the endocardium, resulting in subendocardial ischemia. There is some evidence that pacing at typical fixed pacemaker rates may actually cause patients with aortic stenosis to lose cardiac output and have decreased perfusion pressure.

On the other hand, the patient with aortic insufficiency has regurgitation backwards into the ventricle. A slow rate allows more blood to flow backwards, increasing volume and ventricular pressure. This also restricts blood flow from the coronary arteries to the endocardium, again resulting in subendocardial ischemia. A faster paced rate may help control the condition. Of course, the best rate for perfusing the endocardium for either condition varies considerably between patients.

Rate requirements will probably change a great deal when a prosthetic valve replacement is made.

Typically, any patient with valvular heart disease who requires a pacemaker could benefit from the flexibility a rate-programmable pacemaker offers in this complex, unpredictable disorder.



CHANGING RATE TO ENHANCE THE METABOLIC STATE THROUGH IMPROVED HEMODYNAMICS

Conditions of disease, or certain medical treatments, can affect a patient's metabolic requirements. Pacemaker patients are, because of their age and underlying heart disease, prone to various medical problems, including myocardial infarction, angina and congestive heart failure.

By having the ability to alter the diseased or ill patient's heart rate, the physician can optimize the rate for maximum cardiac output and organ perfusion without affecting (or with minor effects) on myocardial oxygen uptake. Also, in some MI patients a rate can be found which produces increased cardiac output with decreased left ventricular filling pressure. Rate changes may also affect and improve a patient's mental state and enhance the ability to perform even mild exercise. When a pacemaker is implanted, the patient is ill (i.e. bed-ridden). An adequate rate under those conditions may not be adequate when the patient is up and about.

USE OF RATE PROGRAMMABLE PACEMAKERS TO CONTROL VENTRICULAR ARRHYTHMIAS

Ectopic ventricular activity can be suppressed by permanent pacing. However, the slowest paced rate at which ventricular arrhythmias will be controlled is unpredictable, and changeable. It is not unusual for the rate at which PVC's occur to change as the patient's underlying heart disease progresses.

Pacing in the presence of PVC's often involves considerable adjusting of rate as the physician determines the paced rate which will be just slightly higher than the rate at which the ectopic foci discharge. This rate may involve a compromise, for an optimal rate for achieving maximal cardiac output may not coincide with the best rate for suppressing ectopic activity. Indeed some pacemaker rates tend to excite reentry pathways causing the extra-systole.

For these reasons, having the opportunity to change rate can assist the physician in arrhythmia control.

Medtronic

Helping You
Help The Pacemaker Patient

MEDTRONIC'S XYREL® -VP PACING SYSTEM

Offering you simplicity, ease of operation, and seven pacing rates plus one diagnostic rate for patient safety.

The Xyrel®-VP. It's as easy to program as 1, 2, 3.

1. Set the desired pacing rate.
2. Position the programmer over the pacemaker.
3. Press and release the program activate button.*

Constant Energy—A programmed pulse width increase as battery voltage declines provides for constant pacemaker energy output throughout its effective service life.

Constant Rate—Xyrel®-VP pacemaker rate stays at the rate at which you programmed it. It won't decrease as battery voltage slowly drops. However, once voltage declines to the point at which the pacemaker should be replaced, an easily detected rate decrease occurs over one to six months (typically). There are many other performance and safety features that are part of every Xyrel®-VP pulse generator.

*To avoid inadvertent programming to the 30 ppm rate, an additional step is necessary when this rate is desired.

Send in the coupon for details. Or see your local Medtronic representative.

MEDTRONIC IMPLANTABLE PULSE GENERATORS

INTENDED USES Ventricular pacing using an implantable ventricular pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation or conduction disorders leading to bradyarrhythmias, tachyarrhythmias and heart block (see product labeling for detailed list of intended uses).

CONTRAINDICATIONS There are no known contra-indications to the use of pacing as a therapeutic modality for the control of heart rate. The patient's age and medical condition, however, may dictate the particular pacing systems and implantation procedure used by the physician.

WARNINGS Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of unipolar pulse generators or bipolar pulse generators implanted in the unipolar mode because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator.

PRECAUTIONS The physician should be aware that all pulse generators will ultimately cease to function, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, and elevated thresholds, and that proper operation may be affected by electrical interference from equipment using electrical energy, or medical complications.

SIDE EFFECTS Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.

MEDTRONIC HAS COMPILED MORE COMPLETE INFORMATION ON THE APPLICATIONS OF RATE PROGRAMMABILITY TO PACEMAKER PATIENTS

If you would like a copy of Medtronic's information guide on the applications of rate programmability where permanent ventricular pacing is indicated, please send in the coupon below.

Mail To: **Medtronic, Inc., 3055 Old Highway Eight, P.O. Box 1453 Minneapolis, MN 55440 USA**

- ☐ I would like more information on the applications of rate programmability.
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Helping You
Help The Pacemaker Patie

The new generation
beta blocker
for hypertension
New
Lopressor™
metoprolol tartrate

Adds a measure of selectivity to other beta-blocker advantages in treating hypertension

New
Lopressor™
metoprolol tartrate

Decreases blood pressure with less potential for bronchospasm

Lopressor, a relatively selective beta blocker, is an effective and well-tolerated antihypertensive.

Lopressor exerts a preferential effect on the beta receptors involved in lowering blood pressure and has less effect on beta receptors not involved in blood pressure control.

It concentrates its action on beta receptors in the heart (β_1) and leaves beta receptors in the lungs (β_2) relatively unblocked.

WARNING: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. However, Lopressor may be prescribed with caution for hypertensives with asthma or COPD who do not respond to, or cannot tolerate, other antihypertensive therapy. Since β_1 selectivity is not absolute and diminishes with increased dosage, a β_2-stimulating agent should be administered concomitantly, and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in three doses daily, instead of two, to avoid the higher plasma levels associated with the longer dosing interval.

Logical complement to a diuretic

The effectiveness of Lopressor combined with a diuretic was demonstrated in a study* of 15 hypertensive patients whose blood pressure was reduced on a thiazide alone, and still further reduced when metoprolol was added to the regimen. On a regimen of 100 mg hydrochlorothiazide daily, the maximal response was a mean supine blood pressure reduction of 19/10 mmHg —from a placebo-treatment baseline level of 169/115 mmHg. Following four weeks during which metoprolol 50 mg b.i.d. was added to the regimen, there was a further decrease of 17/13 mmHg.

Mild, transient side effects

Most side effects are mild and transient. The most frequently reported adverse reactions (which

*Mitenko P, McKenzie J: Unpublished study. Data on file, Geigy Pharmaceuticals and available on request.

Usually lacks the side-effect problems of the sympathetic inhibitors

occurred in approximately ten out of 100 patients) are tiredness and dizziness. Depression and diarrhea have occurred in about five out of 100.

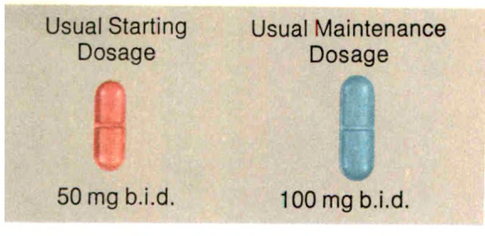
Lopressor usually lacks the side effects of the sympathetic inhibitors which may cause sedation, sexual dysfunction and postural hypotension.

Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.

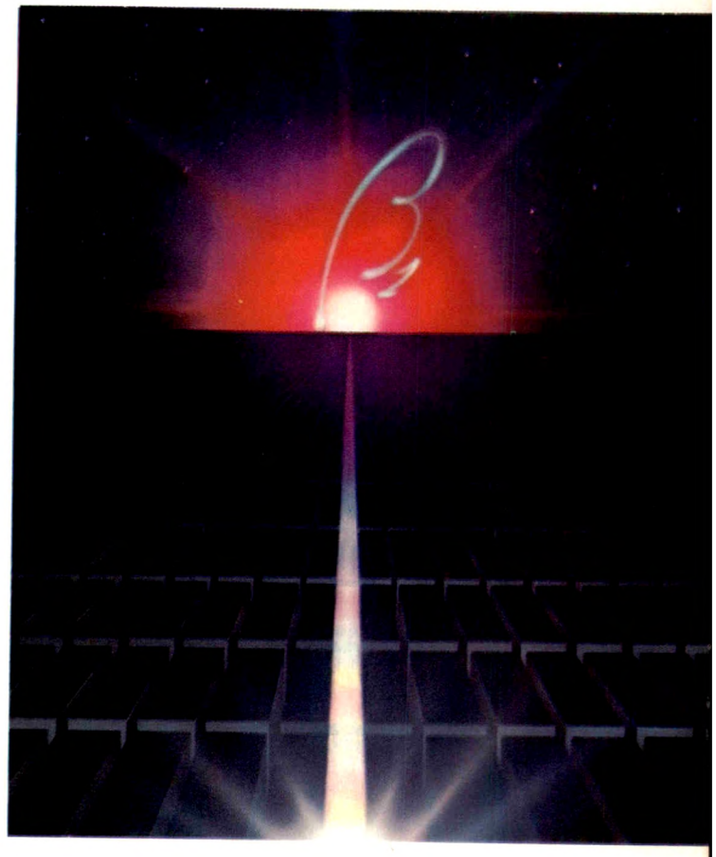
There have been reports of exacerbations of angina pectoris and, in some cases, myocardial infarction following *abrupt* cessation with other beta blockers. Even in the absence of overt angina pectoris, when discontinuing therapy, withdraw Lopressor slowly.

Simple b.i.d. dosage

Patient adherence to the regimen is likely with Lopressor because of its easy-to-remember b.i.d. dosage schedule. The usual starting dosage is one 50-mg tablet twice a day. The usual maintenance dosage is one 100-mg tablet twice a day.



While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. For further details, please see brief summary of prescribing information.



Extensive experience worldwide

Over 240,000 patients have been treated with metoprolol in 21 different countries.

Please see last page for brief summary of prescribing information.

The relatively selective beta blocker for hypertension–with simple b.i.d. dosage

Geigy

Lopressor™
brand of metoprolol tartrate

An antihypertensive beta-blocking agent

Indications Lopressor, brand of metoprolol tartrate, is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor, brand of metoprolol tartrate, is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor, brand of metoprolol tartrate, should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor, brand of metoprolol tartrate, therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor, brand of metoprolol tartrate, should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$ selectivity, however, Lopressor, brand of metoprolol tartrate, may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since $beta_1$ selectivity is not absolute, a $beta_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in three doses daily, instead of two, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor, brand of metoprolol tartrate, should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor, brand of metoprolol tartrate, plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor, brand of metoprolol tartrate, should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities, Raynaud's disease, palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor, brand of metoprolol tartrate, during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor, brand of metoprolol tartrate, should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. $Beta_1$ selectivity diminishes as dosage of Lopressor, brand of metoprolol tartrate, is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

667290 (8/78) C78-3

Before prescribing or administering, please consult complete product information.

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Retrograde Block During Dual Pathway Atrioventricular Nodal Reentrant Paroxysmal Tachycardia

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PABLO DENES, MD, FACC
KENNETH M. ROSEN, MD, FACC

Chicago, Illinois

There are limited reported data regarding the occurrence of retrograde block during dual pathway atrioventricular (A-V) nodal reentrant paroxysmal tachycardia. This study describes two patients with this phenomenon. The first patient had 2:1 and type 1 retrograde ventriculoatrial block during the common variety of A-V nodal reentrance (slow pathway for anterograde and fast pathway for retrograde conduction). Fractionated atrial electrograms suggested that the site of block was within the atria. The second patient had type 1 retrograde block (between the A-V node and the low septal right atrium) during the unusual variety of A-V nodal reentrance (slow pathway for retrograde and fast pathway for anterograde conduction). The abolition of retrograde block by atropine suggested that the site of block was within A-V nodal tissue. Both cases demonstrate that intact retrograde conduction is not necessary for the continuation of A-V nodal reentrant paroxysymal tachycardia. Case 2 supports the hypothesis that the atria are not a requisite part of the A-V nodal reentrant pathway.

Whether the atria are necessary for the occurrence of atrioventricular (A-V) nodal reentrance in man has remained controversial.[1–5] The observation of spontaneous failure of retrograde conduction during A-V nodal reentrant paroxysmal tachycardia has been cited as evidence that the atria are not a requisite part of the reentrant pathway.[2,3] However, there have been only two cases reported in which intracardiac electrode studies suggested such a phenomenon.[2,3] In neither was the mechanism of the tachycardia clearly documented or the site of retrograde block delineated. Therefore, there is a possibility that the site of block was intraatrial.

In this study, we describe two patients who had second degree retrograde block during electrophysiologically demonstrated dual pathway A-V nodal reentrant paroxysmal tachycardia. In one patient the site of block was intraatrial, in the other it was probably A-V nodal. The electrophysiologic and clinical implications of these findings are discussed.

Methods

Electrophysiologic studies: Electrophysiologic studies were performed with the patients in the nonsedated state after cardiac medications had been discontinued for at least 72 hours. Informed written consent was obtained before study. In both patients, a quadripolar electrode catheter was passed percutaneously and advanced across the tricuspid valve for His bundle recording and ventricular pacing.[6] In Patient 1, a hexapolar catheter was also advanced to the coronary sinus from an antecubital vein. The distal two electrodes (tip) were used to record left atrial electrograms, the middle two electrodes were used to stimulate the high right atrium and the proximal two electrodes were used to record high right atrial electrograms. In Patient 2, a second quadripolar catheter was advanced to the high right atrium from an antecubital vein. The distal two electrodes were used for atrial pacing and the proximal two electrodes were used to record high right atrial electrograms.

From the Section of Cardiology, Department of Medicine, Abraham Lincoln School of Medicine, University of Illinois College of Medicine, Chicago, Illinois. This study was supported in part by Cardiology Training Grant PHS-HL 05879-08 from the U.S. Public Health Service, Bethesda, Maryland and Conduction Disease Grant PHS-HL 18794-03 from the National Institutes of Health, Bethesda, Maryland. Manuscript received February 9, 1978; revised manuscript received April 18, 1978, accepted April 19, 1978.

Address for reprints: Robert A. Bauernfeind, MD, Cardiology Section, University of Illinois Hospital, PO Box 6998, Chicago, Illinois 60680.

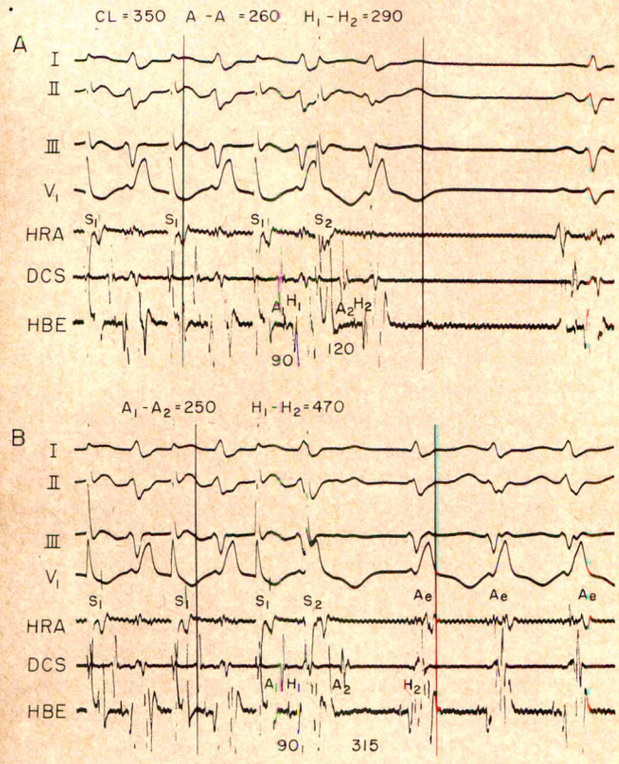

FIGURE 1. Patient 1. Recordings showing responses to atrial extrastimuli before procainamide. Shown are electrocardiographic leads I, II, III and V_1, as well as high right atrial (HRA), distal coronary sinus (DCS) and His bundle (HBE) electrograms. A_1 and H_1 are atrial and His bundle responses to driving stimuli (S_1), A_2 and H_2 are the corresponding responses to the test stimuli (S_2). A_e designates atrial echoes during A-V nodal reentrant paroxysmal tachycardia. Time lines are at 1 second intervals and the paper speed is 100 mm/sec in this and subsequent illustrations. A_1-A_2 and H_1-H_2 intervals are listed at the top and A_1-H_1 and A_2-H_2 intervals at the bottom of each panel. In **panel A,** at an A_1-A_2 coupling interval of 260 msec, the A_2-H_2 interval was 120 msec, and no atrial echoes resulted. In **panel B,** at an A_1-A_2 coupling interval of 250 msec, the A_2-H_2 interval was 315 msec, and sustained A-V nodal reentrant paroxysmal tachycardia, with a cycle length (CL) of 320 msec, resulted.

In both patients multiple electrocardiographic leads and intracardiac electrograms were recorded on a multichannel oscilloscopic recorder (Electronics for Medicine DR-16) at paper speeds of 100 and 200 mm/sec. Electrical stimuli were provided by a programmable digital stimulator (manufactured by M. Bloom, Narberth, Pennsylvania) and were approximately twice diastolic threshold and 2 msec in duration.

Anterograde and retrograde conduction were evaluated in both patients with incremental pacing and extrastimulus techniques.[7,8] In Patient 1, the quadripolar catheter was removed after the initial study. The hexapolar catheter was repositioned (with the distal two electrodes in the right ventricular apex and the proximal four electrodes in the high right atrium) and secured in place. The patient was restudied on a subsequent day after receiving oral procainamide, 3 g daily. Patient 2 was restudied immediately after administration of atropine sulfate, 1 mg intravenously.

Definitions: HRA_1, A_1, DCS_1, H_1 and V_1 were, respectively, the high right atrial, low septal right atrial, distal coronary sinus (left atrial), His bundle and ventricular responses to driven stimuli (S_1). HRA_2, A_2, DCS_2, H_2 and V_2 were the high right atrial, low septal right atrial, left atrial, His bundle and ventricular responses to the extrastimulus (S_2). Similar subscripts were employed to designate the responses to a second extrastimulus (S_3). HRA_e, A_e, DCS_e, H_e and V_e were the high right atrial, low septal right atrial, left atrial, His bundle and ventricular electrograms of single echo beats and also repetitive beats during paroxysmal supraventricular tachycardia.

Conduction intervals, refractory periods, anterograde echo zones and critical A-H intervals (for atrial echo and supraventricular tachycardia induction) were measured and defined as previously described.[8–12] Retrograde echo zones and critical ventriculoatrial (V-A) intervals (for ventricular echo and supraventricular tachycardia induction) were also measured as previously described.[13,14] Anterograde dual A-V nodal pathways were demonstrated when discontinuous A_1-A_2, H_1-H_2 curves were generated with atrial extrastimulus testing at any driven cycle length.[12] Similarly, retrograde dual A-V nodal pathways were demonstrated when discontinuous V_1-V_2, A_1-A_2 curves were generated with ventricular extrastimulus testing.[13] Effective refractory periods of anterograde and retrograde fast and slow A-V nodal pathways were measured and defined as previously described.[12,13] A-V nodal reentrant paroxysmal tachycardia was diagnosed when previously reported diagnostic criteria were met.[15]

Results

Patient 1

The patient was a 52 year old woman with angiographically documented mitral valve prolapse and a 22 year history of recurrent paroxysmal supraventricular tachycardia. Electrocardiograms during sinus rhythm revealed only nonspecifc S-T and T wave changes. Paroxysmal supraventricular tachycardia occurred at rates of approximately 190 beats/min and was characterized by a right bundle branch block pattern and no visible P waves in the surface electrocardiograms.

His bundle recordings during sinus rhythm revealed normal P-A, A-H and H-V intervals (38, 52 and 32 msec, respectively) with normal QRS configuration. With incremental atrial pacing, right bundle branch block was noted at paced rates of 120 or more beats/min. As paced rates were increased from 100 to 210/min, A-V conduction remained intact, although A-H intervals gradually increased from 60 to 210 msec. At an atrial paced rate of 220/min, the A-H interval suddenly prolonged to 340 msec (suggesting failure of a fast A-V nodal pathway), and supraventricular tachycardia was induced.

Atrial extrastimulus studies at a driven cycle length of 500 msec generated a continuous A_1-A_2, H_1-H_2 curve with A-V nodal conduction limited only by an atrial functional refractory period of 250 msec. The maximal A_2-H_2 interval achieved was 190 msec, and no A-V nodal reentrant atrial echoes were observed. When the driven cycle length was reduced to 350 msec, a discontinuous A_1-A_2, H_1-H_2 curve was generated because of a sudden jump in the A_2-H_2 interval at an A_1-A_2 coupling interval of 250 msec (Fig. 1). The effective refractory period of the fast pathway was thus 250 msec, whereas conduction in the slow pathway was limited only by an atrial functional refractory period of 240 msec. The demonstration of a discontinuous curve only at the shorter driven cycle length reflected a decrease in the atrial functional refractory period. Induction of supraventricular tachycardia coincided with anterograde failure of the fast pathway (Fig. 1).

With incremental ventricular pacing, intact V-A conduction was present at paced rates as fast as 190 beats/min. However, at a paced rate of 200/min, V-A Wenckebach peri-

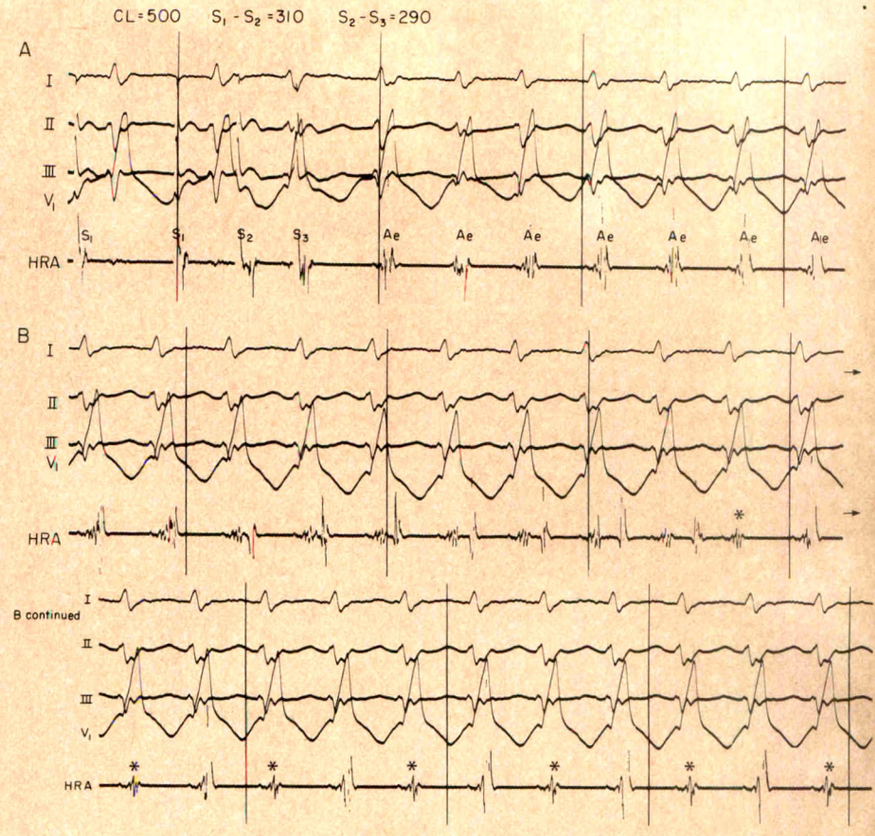

FIGURE 2. Patient 1. Recordings after procainamide, demonstrating intraatrial block during paroxysmal supraventricular tachycardia. A temporary catheter is now in place, with its tip anchored in the right ventricular apex. In each panel, a high right atrial electrogram is recorded (note the absence of ventricular electrical activity during the first two conducted QRS complexes in **panel A**). In **panel A,** S_1, S_2 and S_3 designate driving stimuli, the first test stimulus and the second test stimulus, respectively. The driving cycle length, S_1-S_2 interval and S_2-S_3 interval are listed at the top of the panel. When S_3 was conducted to the ventricles with a long delay (slow pathway), sustained A-V nodal reentrant paroxysmal tachycardia resulted. The cycle length of the tachycardia was 355 msec. During the tachycardia, atrial electrograms and QRS complexes were simultaneous. **Panel B** shows continuous recordings during induced supraventricular tachycardia. The high right atrial deflections first widened and then split into two fractions. The first fraction remained simultaneous with each QRS complex; the second fraction was progressively delayed, terminating in block (denoted by **asterisk**). As the tachycardia continued, only a part of the high atrial deflection occurred with every other QRS complex (denoted by **asterisks**). Abbreviations as in Figure 1.

odicity was noted. Ventricular extrastimulus studies at a driven cycle length of 500 msec generated a continuous V_1-V_2, A_1-A_2 curve. The effective refractory period of the V-A conduction system was 255 msec, and no ventricular echoes were observed.

The cycle length of the induced supraventricular tachycardia ranged from 295 to 330 msec (mean 325). During supraventricular tachycardia, all QRS complexes were conducted with a right bundle branch block pattern, and atrial electrograms occurred simultaneously with the QRS complexes (Fig. 1B).

When the patient was restudied after oral administration of procainamide, the same sustained supraventricular tachycardia could be induced with atrial extrastimuli only when sufficient A-V conduction delay was achieved (Fig. 2A). The mean cycle length of the tachycardia was 355 msec, and high right atrial electrograms again occurred simultaneously with QRS complexes. However, during this supraventricular tachycardia, type I second degree block and 2:1 block occurred between fractions of high right atrial electrograms without terminating the induced rhythm (Fig. 2B).

Comment: A-V nodal reentrant paroxysmal tachycardia of the common variety (utilizing anterograde slow and retrograde fast pathway conduction) was diagnosed in this patient on the basis of several factors: (1) Induction of supraventricular tachycardia related to achievement of a critical A-H delay during both incremental atrial pacing and atrial extrastimulus testing.[11] (2) Demonstration of a discontinuous A_1-A_2, H_1-H_2 curve, suggesting the presence of anterograde dual A-V nodal pathways, with induction of supraventricular tachycardia relating to anterograde block in the fast pathway.[12] (3) Atrial activation (high right, low right and coronary sinus) occurring simultaneously with the onset of ventricular activation during induced supraventricular tachycardia.[15,16] This latter observation suggested that multiple atrial sites were not part of the reentrant circuit.

During the study after administration of procainamide, the atrial electrodes were fluoroscopically located in the high right atrium and did not record ventricular electrical activity to any significiant degree. V-A conduction was intact during induced supraventricular tachycardia, as indicated by the simultaneous recording of an atrial electrogram with each QRS complex. However, another segment of atrial tissue in proximity to the electrodes must have been located beyond a site of retrograde conduction delay (type I second degree and 2:1 block). The site of retrograde block was presumably intraatrial, and probably was located within the recording area of the high right atrial electrodes. It is also possible that the block occurred at a more distal site in the atria (but manifested itself as a delay in a portion of the high right atrial electrogram). It is clear that the site of conduction delay was proximal to the reentrant circuit because neither type I second degree nor 2:1 retrograde block terminated the induced supraventricular tachycardia.

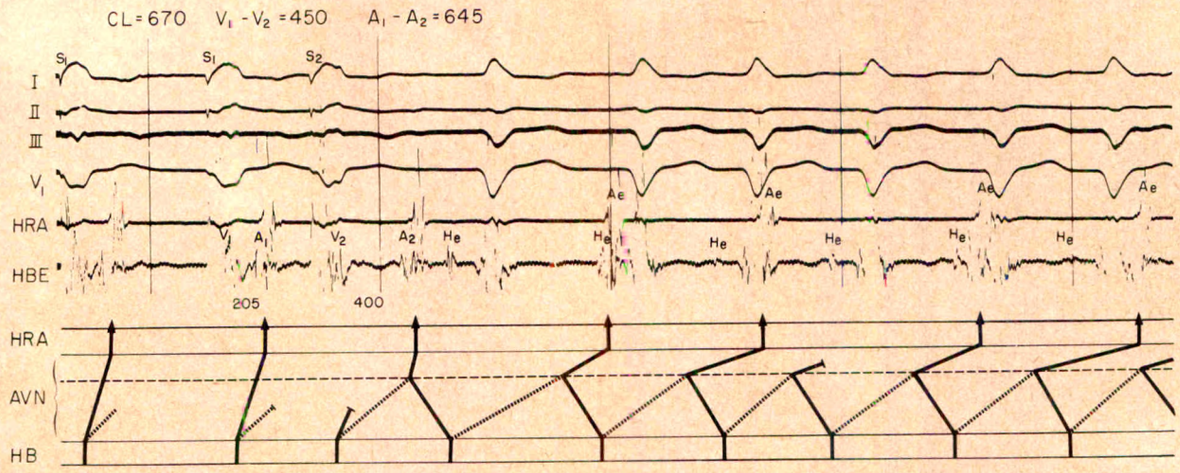

FIGURE 3. Patient 2. Top, recordings showing induction of supraventricular tachycardia with a ventricular extrastimulus before atropine. V_1 and A_1 are ventricular and atrial responses to driving stimuli (S_1); V_2 and A_2 are the corresponding responses to the test stimulus (S_2). H_e and A_e are, respectively, His bundle and atrial depolarizations during A-V nodal reentrant paroxysmal tachycardia. V_1-V_2 and A_1-A_2 intervals are listed at the top and V_1-A_1 and V_2-A_2 intervals at the bottom of the panel. At a V_1-V_2 coupling interval of 450 msec, V_2-A_2 was 400 msec, A_1-A_2 was 645 msec, and supraventricular tachycardia was induced. The mean cycle length (CL) of the tachycardia was 515 msec, and each QRS complex had a left bundle branch block configuration identical to that of conducted beats during sinus rhythm and atrial pacing. During paroxysmal supraventricular tachycardia there was 3:2 conduction between QRS complexes and atrial electrograms. **Bottom,** diagram of the presumed mechanisms of tachycardia and retrograde block. The steps of the ladder represent high right atrial (HRA), A-V nodal (AVN) and His bundle (HB) conduction. The **dashed horizontal line** represents the proximal common pathway, which was located within the A-V node (see text for discussion). The **solid** and **dashed diagonal lines** within the lower part of the A-V nodal level represent fast and slow A-V nodal pathways, respectively. HBE = His bundle electrogram.

Patient 2

The patient was a 64 year old man with hypertensive heart disease and recurrent dizziness and palpitations. Electrocardiograms revealed first degree A-V block (P-R interval, 0.26 second) and atypical left bundle branch block (S wave in lead V_6).

His bundle recordings during sinus rhythm with left bundle branch block revealed normal P-A and A-H intevals (42 and 89 msec, respectively) and a prolonged H-V interval (105 msec [normal 31 to 55]). With incremental atrial pacing, type I second degree A-V block occurred proximal to the His bundle potential at a paced rate of 140 beats/min. Atrial extrastimulus studies at a driven cycle length of 600 msec revealed a discontinuous A_1-A_2, H_1-H_2 curve due to a sudden jump in the A_2-H_2 interval at an A_1-A_2 coupling interval of 320 msec. The effective refractory period of the fast pathway was 320 msec, whereas conduction on the slow pathway was limited only by an atrial functional refractory period of 270 msec. Although A_2-H_2 intervals as long as 335 msec were achieved with slow pathway conduction, no atrial echoes were observed.

Incremental ventricular pacing revealed intact V-A conduction at paced rates up to 100 beats/min. At paced rates of 110/min or greater, V-A Wenckebach periods occurred, and a single A-V nodal reentrant ventricular echo or supraventricular tachycardia was induced whenever the last paced beat was conducted with a V-A interval of 345 msec or longer.

Ventricular extrastimulus studies at a driven cycle length of 670 msec generated a discontinuous V_1-V_2, A_1-A_2 curve due to a sudden jump in the H_2-A_2 interval at a V_1-V_2 coupling interval of 510 msec. The effective refractory period of the retrograde fast pathway was 510 msec, whereas that of the retrograde slow pathway was 410 msec. All beats conducted by way of the slow pathway resulted in a single A-V nodal reentrant ventricular echo or supraventricular tachycardia (Fig. 3).

All beats during induced supraventricular tachycardia were conducted with a left bundle branch block pattern identical to that present during sinus rhythm. The cycle length of tachycardia ranged from 490 to 550 msec (mean 515). During each episode of supraventricular tachycardia there was 3:2 retrograde conduction to the atria in a Wenckebach pattern (Fig. 3) without significant effect on the cycle length of tachycardia. Each episode of supraventricular tachycardia eventually terminated spontaneously because of block in the retrograde slow pathway.

After administration of atropine, retrograde conduction improved and was intact at paced rates to 170 beats/min. However, at a paced rate of 170/min, supraventricular tachycardia was induced each time the last paced beat was conducted with a V-A interval of 340 msec or longer (Fig. 4). Atropine shortened the cycle length of induced tachycardias to 330 msec (by shortening intra A-V nodal conduction time) and eliminated block in retrograde conduction during the tachycardias.

Comment: A-V nodal reentrant paroxysmal tachycardia of the unusual variety (utilizing retrograde slow and anterograde fast pathway conduction) was diagnosed in this patient on the basis of the following factors: (1) Induction of supraventricular tachycardia related to achievement of a critical V-A delay during both ventricular pacing and ventricular extrastimulus testing.[13,16] (2) Demonstration of a discontinuous V_1-V_2, A_1-A_2 curve, suggesting the presence of retrograde dual A-V nodal pathways, with induction of supraventricular tachycardia relating to retrograde block in the fast pathway.[13] (3) The presence of a normal retrograde atrial activation sequence during induced supraventricular tachycardia.[17]

The site of retrograde block during supraventricular tachycardia was between conducted QRS complexes and the low atrial septum (as recorded in the His bundle electrogram). It also must have been proximal to the

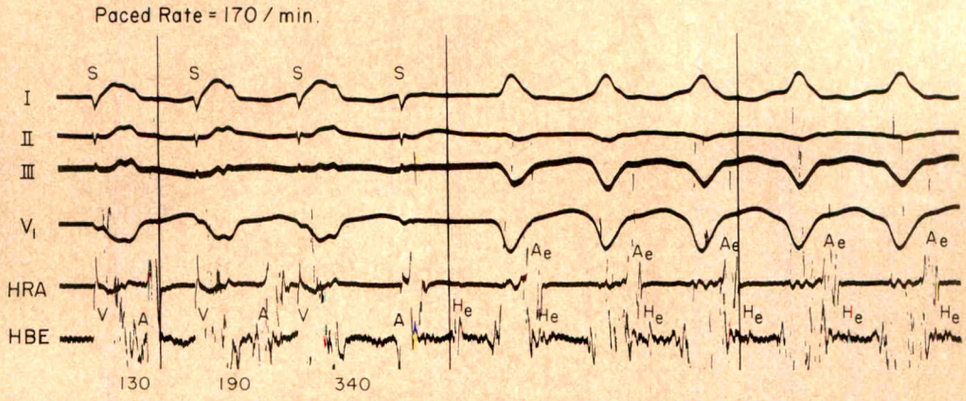

FIGURE 4. Patient 2. Recordings showing induction of supraventricular tachycardia with ventricular pacing after atropine. Ventriculoatrial (V-A) intervals are listed at the bottom of the panel. The first three stimuli capture the ventricles (the fourth does not) and are conducted to the atria with progressively long V-A intervals. The third stimulus was conducted with a V-A interval of 340 msec and resulted in supraventricular tachycardia. This tachycardia was characterized by a cycle length of 330 msec and a QRS configuration of left bundle branch block. There was 1:1 retrograde conduction to the atria. HBE = His bundle electrogram; HRA = high right atrial.

reentrant pathway because the occurrence of block did not terminate the tachycardia. Furthermore, abolition of the block with atropine suggests that the site of retrograde block was in the A-V node or in transitional atrionodal tissue.

Discussion

Surface electrocardiograms during paroxysmal supraventricular tachycardia are usually characterized by a P wave for each QRS complex (although frequently the two occur simultaneously and the P waves cannot be clearly identified). Exceptions have been reported, however, beginning with the study of Katz and Pick,[18] who observed an episode characterized by type I second degree block between conducted QRS complexes and P waves. Pick and Langendorf[19] observed A-V dissociation in a case of paroxysmal supraventricular tachycardia, and Zeft and McGowan[20] reported on a patient with the same tachycardia and only one P wave for every two QRS complexes. Additional examples of block between conducted QRS complexes and P waves have been reported.[21–23] These cases, although lacking electrophysiologic documentation, probably represent examples of A-V nodal reentrant paroxysmal tachycardia because the presence of retrograde block eliminates atrial or sinus reentry, as well as A-V reentrance utilizing an extranodal pathway, as alternative possibilities.[3,15] If one assumes that these reported cases are examples of A-V nodal reentry, they suggest that the bulk of atrial tissue is not a necessary part of the A-V nodal reentrant pathway.

There have been only two previous reports of patients with spontaneous failure of retrograde conduction during supraventricular tachycardia in whom electrophysiologic studies suggested A-V nodal reentry as the mechanism of arrhythmia. Wu et al.[2] reported on a patient with anterograde dual A-V nodal pathways and A-V dissociation during an accelerated supraventricular rhythm (rate 80 beats/min), but they could not exclude the possibility that the rhythm was nonparoxysmal junctional tachycardia. More recently, Wellens et al.[3] reported on a patient with 2:1 retrograde conduction during induced supraventricular tachycardia, but they did not define in detail the mechanism of the tachycardia or document the site of retrograde block.

Site of retrograde block during tachycardia: Our two patients had well documented dual pathway A-V nodal reentrant paroxysmal tachycardia with retrograde block during the tachycardia. Furthermore, in each patient, a site of retrograde block was suggested by intracardiac recordings. In Patient 1, type I second degree and 2:1 block occurred between fractions of the high right atrial electrogram. Thus the site of retrograde block in that patient was within the atria. It is likely that the administration of procainamide, which has been shown to increase atrial refractoriness, played a role in the development of this block.[24] In Patient 2, type I second degree block occurred between conducted QRS complexes and low septal right atrial electrograms. The ability of atropine to abolish block in this patient, despite a considerable decrease in cycle length of paroxysmal supraventricular tachycardia (from 515 to 320 msec), strongly suggests that the site of retrograde block was within A-V nodal tissue.[25] Although Dhingra et al.[26,27] demonstrated that atropine may slightly decrease atrial refractoriness in man, changes of the magnitude required to postulate reversal of intraatrial block in this patient have not been observed. Therefore, our study suggests that retrograde block during A-V nodal reentrant paroxysmal tachycardia may occur either within the atria or within the A-V node.

Are the atria a necessary part of the reentrant pathway? Previously reported cases[2,3] of spontaneous retrograde block between conducted QRS complexes and atrial electrograms during paroxysmal supraventricular tachycardia have been cited as evidence that the atria are not a requisite part of the reentrant pathway. The same conclusion was reached by Josephson and Kastor,[1] who preempted atrial depolarization during A-V nodal reentrant paroxysmal tachycardia by introducing atrial extrastimuli before anticipated atrial

echoes. However, Zipes et al.[4] argued that depolarization of a small rim of atrial tissue may not be recorded by routine intracardiac recording techniques and described two patients with apparent A-V dissociation in whom careful exploration of the atrial septum revealed that the local atrial electrograms were associated with conducted QRS complexes. Therefore, patients with retrograde block during paroxysmal supraventricular tachycardia might have intraatrial block (and the atria might still be a necessary component of the circus movement). Our Case 1, in which there was retrograde intraatrial block during A-V nodal reentrant paroxysmal tachycardia, supports the hypothesis of Zipes et al. Thus, the demonstration of retrograde block during A-V nodal reentrant paroxysmal tachycardia does not necessarily mean that some atrial tissue is not involved in the reentrant circuit.

However, our Case 2 suggests that the atria are not always a necessary part of the reentrant pathway. This patient had the unusual variety of A-V nodal reentrant paroxysmal tachycardia induced by ventricular pacing. Tachycardia of this type requires retrograde block of an impulse in a fast A-V nodal pathway with retrograde conduction over a slow A-V nodal pathway to a proximal common pathway. Retrograde conduction then usually continues from the proximal common pathway to the body of the atria while anterograde conduction occurs over the fast A-V nodal pathway to a distal common pathway (which is probably located in the distal part of the A-V node).[3] From the distal common pathway, the impulse reenters the retrograde slow A-V nodal pathway as well as continuing in anterograde manner to the ventricles. In our Case 2 type I second degree block occurred between the proximal common pathway and the low septal right atrial recording site. Because block was abolished by atropine, the site of block was probably located within the A-V node or in transitional atrionodal tissue. The continuation of the tachycardia despite the occurrence of retrograde block indicates that the proximal common pathway must have been at a more distal level of the A-V node. These data suggest that the atria were not a necessary part of the reentrant pathway.

Clinical implications: Our observations relate to prediction of which patients with anterograde dual A-V nodal pathways will have atrial echoes or paroxysmal supraventricular tachycardia. Our laboratory and others[28,29] have suggested that A-V nodal reentry can occur only in patients with intact retrograde conduction (as assessed with ventricular pacing). This study demonstrates that it is possible to have A-V nodal reentrance with retrograde block (atrial or A-V nodal) proximal to the site of reentrance. Thus occasional patients could have poor (or even absent) retrograde conduction and yet be capable of having A-V nodal reentrant paroxysmal tachycardia.

A final point relates to electrocardiographic differential diagnosis. A tachycardia with wide QRS complexes could be either ventricular or supraventricular in origin.[30] Paroxysmal wide QRS tachycardia with retrograde block suggests ventricular tachycardia. However, our Patient 1 had retrograde block during paroxysmal tachycardia with right bundle branch block (rate-dependent), whereas our Patient 2 had retrograde block during paroxysmal tachycardia with left bundle branch block (preexisting). Therefore, these patients demonstrate that a tachycardia of this type could be A-V nodal reentrant paroxysmal tachycardia.

References

1. **Josephson ME, Kastor JA:** Paroxysmal supraventricular tachycardia. Is the atrium a necessary link? Circulation 54:430–435, 1976
2. **Wu D, Denes P, Dhingra R, et al:** New manifestations of dual A-V nodal pathways. Eur J Cardiol 2:459–466, 1975
3. **Wellens HJJ, Wesdorp JC, Duren DR, et al:** Second degree block during reciprocal atrioventricular nodal tachycardia. Circulation 53:595–599, 1976
4. **Zipes DP, Gaum WE, Genetos BC, et al:** Atrial tachycardia without P waves masquerading as an A-V junctional tachycardia. Circulation 55:253–260, 1977
5. **Schuilenburg RM, Durrer D:** Further observations on the ventricular echo phenomenon elicited in the human heart. Is the atrium part of the echo pathway? Circulation 45:629–638, 1972
6. **Scherlag BJ, Lau SH, Helfant RH, et al:** Catheter technique for recording His bundle activity in man. Circulation 39:13–18, 1969
7. **Goldreyer BN, Bigger JT:** Spontaneous and induced reentrant tachycardia. Ann Intern Med 70:87–98, 1969
8. **Wu D, Denes P, Dhingra R, et al:** The effects of propranolol on induction of A-V nodal reentrant paroxysmal tachycardia. Circulation 50:665–677, 1974
9. **Wit AL, Weiss MB, Berkowitz WD, et al:** Patterns of atrioventricular conduction in the human heart. Circ Res 27:345–359, 1970
10. **Denes P, Wu D, Dhingra R, et al:** The effects of cycle length on cardiac refractory periods in man. Circulation 49:32–41, 1974
11. **Goldreyer BN, Damato AN:** The essential role of atrioventricular conduction delay in the initiation of paroxysmal supraventricular tachycardia. Circulation 43:679–687, 1971
12. **Denes P, Wu D, Dhingra RC, et al:** Demonstration of dual A-V nodal pathways in patients with paroxysmal supraventricular tachycardia. Circulation 48:549–555, 1973
13. **Wu D, Denes P, Amat-y-Leon F, et al:** An unusual variety of atrioventricular nodal reentry due to retrograde dual atrioventricular nodal pathways. Circulation 56:50–59, 1977
14. **Wu D, Denes P, Wyndham C, et al:** Demonstration of dual atrioventricular nodal pathways utilizing a ventricular extra-stimulus in patients with atrioventricular nodal reentrant paroxysmal supraventricular tachycardia. Circulation 52:789–798, 1975
15. **Wu D, Denes P, Amat-y-Leon F, et al:** Clinical, electrocardiographic and electrophysiological observations in patients with paroxysmal supraventricular tachycardia. Am J Cardiol 41: 1045–1051, 1978
16. **Wellens HJJ, Durrer DD:** The role of an accessory atrioventricular pathway in reciprocal tachycardia. Observations in patients with and without the Wolff-Parkinson-White syndrome. Circulation 52:58–72, 1975
17. **Amat-y-Leon F, Dhingra RC, Wu D, et al:** Catheter mapping of retrograde atrial activation. Observations during ventricular pacing and AV nodal reentrant paroxysmal tachycardia. Br Heart J 38: 355–362, 1976
18. **Katz LN, Pick A:** Clinical Electrocardiography. The Arrhythmias. Philadelphia, Lea & Febiger, 1956, p 284
19. **Pick A, Langendorf R:** Differentiation of supraventricular and ventricular tachycardia. Prog Cardiovasc Dis 2:391–407, 1960
20. **Zeft HJ, McGowan RL:** Termination of paroxysmal junctional

tachycardia by right ventricular stimulation. Circulation 40: 919–926, 1969
21. **Coumel P, Motté G, Gourgon R, et al:** Les tachycardies supraventriculaires par rhythme réciproque en dehors du syndrome de Wolff-Parkinson-White. Arch Mal Coeur 63:35–73, 1970
22. **Pick A, Langendorf R, Jedlicka J:** Exit block. Cardiovasc Clin 5: 113–133, 1973
23. **Langendorf R, Pick A:** Manifestations of concealed reentry in the atrioventricular junction. Eur J Cardiol 1:11–21, 1973
24. **Josephson ME, Caracta AR, Ricciutti MA, et al:** Electrophysiologic properties of procainamide in man. Am J Cardiol 33:596–603, 1974
25. **Akhtar M, Damato AN, Caracta AR, et al:** Electrophysiologic effects of atropine on atrioventricular conduction studied by His bundle electrogram. Am J Cardiol 33:333–343, 1974
26. **Dhingra RC, Amat-y-Leon F, Wyndham C, et al:** Electrophysiologic effects of atropine on human sinus node and atrium. Am J Cardiol 38:429–434, 1976
27. **Dhingra RC, Amat-y-Leon F, Wyndham C, et al:** Electrophysiologic effects of atropine on sinus node and atrium in patients with sinus nodal dysfunction. Am J Cardiol 38:848–855, 1976
28. **Denes P, Wu D, Amat-y-Leon F, et al:** The determinants of atrioventricular nodal reentrance with premature atrial stimulation in patients with dual A-V nodal pathways. Circulation 56:253–259, 1977
29. **Bigger JT, Goldreyer BN:** The mechanism of supraventricular tachycardia. Circulation 42:673–688, 1970
30. **Marriott HJL, Myerburg RJ:** Recognition and treatment of cardiac arrhythmias and conduction disturbances. In, The Heart, Arteries and Veins, chap 32C (Hurst JW, Logue RB, Schlant RC, et al., ed). New York, McGraw-Hill, 1974, p 534

Electrophysiologic Observations in a Patient With Bradycardia-Dependent Atrioventricular Block

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In a patient with atrioventricular (A-V) block distal to the His bundle (H), 1:1 A-V conduction with right bundle branch block and an H-V interval of 70 msec was established with atrial pacing at rates of 120 to 150/min, suggesting that the A-V block was bradycardia-dependent. Advanced second degree A-V block distal to the H deflection occurred with atrial pacing at 160/min after completion of A-V nodal Wenckebach periodicity proximal to the H deflection because of the long H-H encompassing the blocked P wave. Atrial extrastimulus testing coupled with sinus rhythm (with A-V block) demonstrated that critical H_1-H_2 intervals of less than 545 msec allowed conduction to the ventricles. The H_2-V_2 interval shortened progressively from 290 to 70 msec with shortening of these critical H_1-H_2 intervals. Atrial extrastimulus testing coupled with an atrial driven cycle length of 500 msec (with intact A-V conduction) revealed block of the H_2 deflection with an H_1-H_2 interval longer than 540 msec.

In conclusion, at critical diastolic intervals, impulses were blocked, creating a state of decreased responsiveness. If a cycle length of subsequent impulses was shorter than the critical diastolic blocking interval, membrane responsiveness gradually improved and conduction resumed. If a cycle length of subsequent impulses was longer than the critical blocking diastolic interval, A-V block was sustained. Blocked impulses continually penetrated to the site of block and reset the state of membrane responsiveness.

Bradycardia-dependent conduction block is an infrequently encountered conduction disturbance, usually reflecting dysfunction within portions of the His-Purkinje system (bundle branch block or His bundle block).[1–10] Although bradycardia-dependent block is usually provoked by a critical slowing of sinus rates, it can also be initiated by the pause after a premature atrial or ventricular contraction. Despite recent interest in this subject, the physiologic mechanisms of bradycardia-dependent block remain unclear. In addition, few electrophysiologic data have been reported concerning bradycardia-dependent block in man.[2,7–10]

In this study, we report results of extensive electrophysiologic studies in a patient with bradycardia-dependent atrioventricular (A-V) block including atrial extrastimulus testing during sinus rhythm (with A-V block) and during atrial driving (with intact A-V conduction). This study provides new observations concerning the electrophysiology of this conduction disturbance.

Report of Case

A 62 year old man was admitted for elective aortic valve replacement because of aortic stenosis and insufficiency. Electrocardiograms before operation revealed sinus rhythm with left ventricular hypertrophy. The aortic valve was successfully replaced with a porcine heterograft. The postoperative course was uneventful

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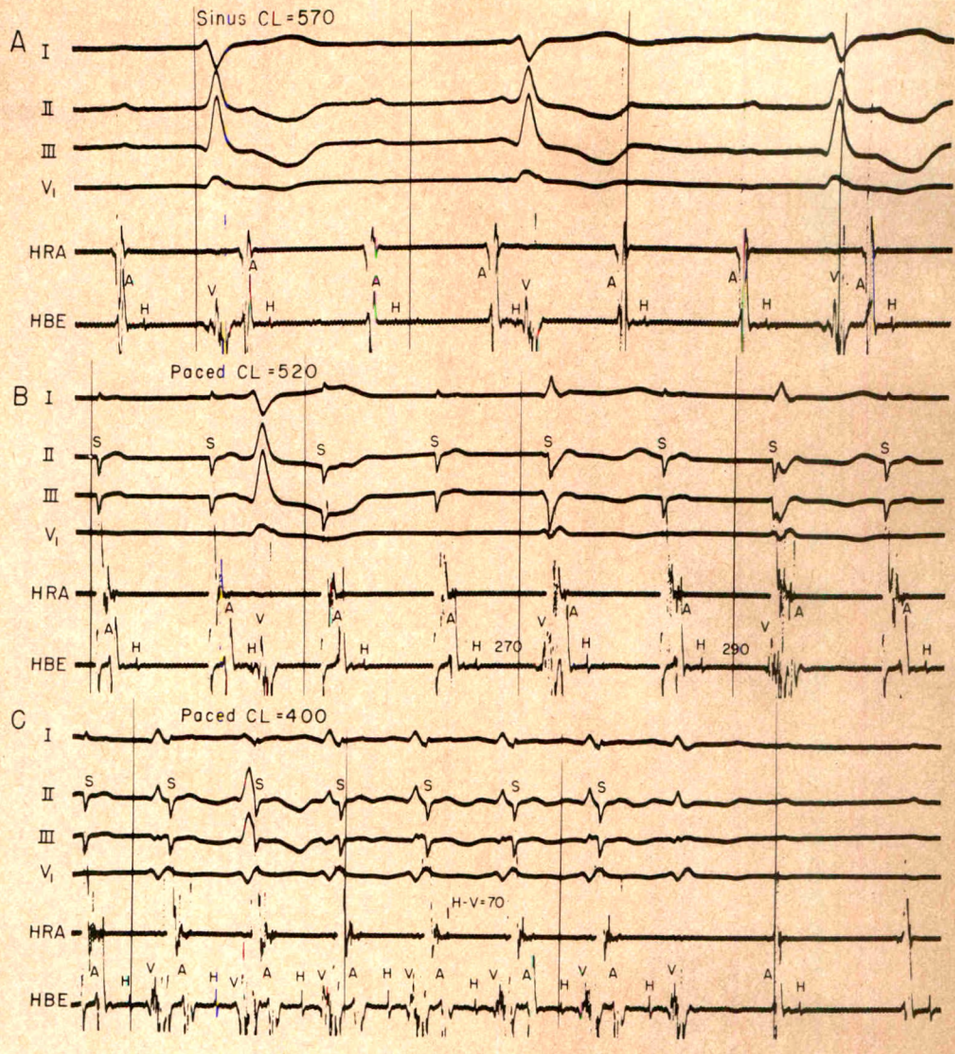

FIGURE 1. Recordings showing complete atrioventricular (A-V) block with resumption of A-V conduction with incremental atrial pacing. Shown are multiple electrocardiographic leads (I, II, III and V_1), high right atrial electrogram (HRA) and His bundle electrogram (HBE). A, H and V are, respectively, atrial, His bundle and ventricular responses recorded in the His bundle electrogram. S represents stimulus artefact. Time lines are at 1 second, and paper speed is 100 mm/sec in this and subsequent illustrations. **A,** complete A-V block distal to the His bundle recording site (H) with a ventricular escape rhythm. Sinus cycle length (CL) is 570 msec, and the escape rhythm cycle length 1,410 msec. The ventricular escape rhythm has a QRS configuration of right bundle branch block and right axis deviation, suggesting an origin in the anterior left ventricle. The A-H interval is 110 msec. **B,** intermittent capture of ventricles with atrial pacing at a cycle length of 520 msec. The first QRS complex is a ventricular escape beat; the second and the third QRS complexes are captured. The capture complexes have a pattern of right bundle branch block with marked prolongation of the H-V interval (270 msec and 290 msec, respectively). **C,** intact A-V conduction with atrial pacing at a cycle length of 400 msec. The H-V interval is 70 msec. Complete A-V block resumes after cessation of rapid atrial pacing.

except for the development of right bundle branch block and transient paroxysmal atrial fibrillation. Ten days after surgery, the patient had a syncopal episode while walking. Electrocardiograms at that time demonstrated complete A-V block with a wide QRS escape rhythm. The patient was treated with a temporary pacemaker immediately after the syncopal episode and with a permanent transvenous right ventricular demand pacemaker the next day. Intact A-V conduction was demonstrated 3 days later, and he has had no further documented episodes of A-V block over a follow-up period of 8 months.

Electrophysiologic Studies

Electrophysiologic studies were performed during insertion of the permanent pacemaker. A percutaneously passed tripolar electrode catheter was positioned across the tricuspid valve for His bundle recording.[11] A second percutaneously passed quadripolar catheter was positioned at the high right atrium for recording of the high right atrial electrograms and right atrial stimulation. Multiple electrocardiographic leads and intracardiac electrograms were simultaneously recorded on a multichannel oscilloscopic photographic recorder (Electronics for Medicine DR-16, White Plains, New York) at paper speeds of 100 and 200 mm/sec. Stimuli were provided by a digital programmable stimulator (manufactured by M. Bloom, Narberth, Pennsylvania) with a strength of approximately twice the diastolic threshold and 2 msec in duration. A-V conduction was evaluated with incremental atrial pacing and atrial extrastimulus testing. Conduction intervals and refractory periods were measured and defined as previously described.[12]

There was complete A-V block during sinus rhythm with an idioventricular escape rhythm showing a pattern of right bundle branch block and right axis deviation. The site of block was distal to the His bundle recording site (distal His bundle or trifascicular) (Fig. 1A). The A-A interval (sinus cycle length) was 570 msec, the A-H interval 110 msec and the V-V interval 1,410 msec.

Atrial pacing at a rate of 115/min (cycle length 520 msec) produced intermittent capture of the ventricles and conducted beats with an H-V interval of 270 to 290 msec (Fig. 1B). At pacing rates of 120 and 150/min (cycle length of 400 to 500 msec), 1:1 A-V conduction was resumed (Fig. 1C), conducted beats having an H-V interval of 70 msec. The conducted beats had a pattern of right bundle branch block and normal axis with occasional left or right axis deviation. Type I second degree block proximal to the H deflection (A-V nodal block) occurred at an atrial paced rate of 160/min (cycle length 375

msec), with 1:1 A-V conduction noted at the onset of pacing (Fig. 2A). However, advanced second degree A-V block distal to the H deflection developed after completion of the Wenckebach sequence because a long H-H interval (560 msec) encompassed the blocked P wave of the Wenckebach period (Fig. 2A). Transient paroxysmal A-V block could also be initiated with a premature ventricular impulse during 1:1 A-V conduction at an atrial paced rate of 120/min (Fig. 2B). Sustained complete A-V block occurred reliably after cessation of rapid atrial pacing (Fig. 2C).

Atrial extrastimulus testing was performed during sinus rhythm (with complete A-V block) (Fig. 3 and 4). H_2 was not

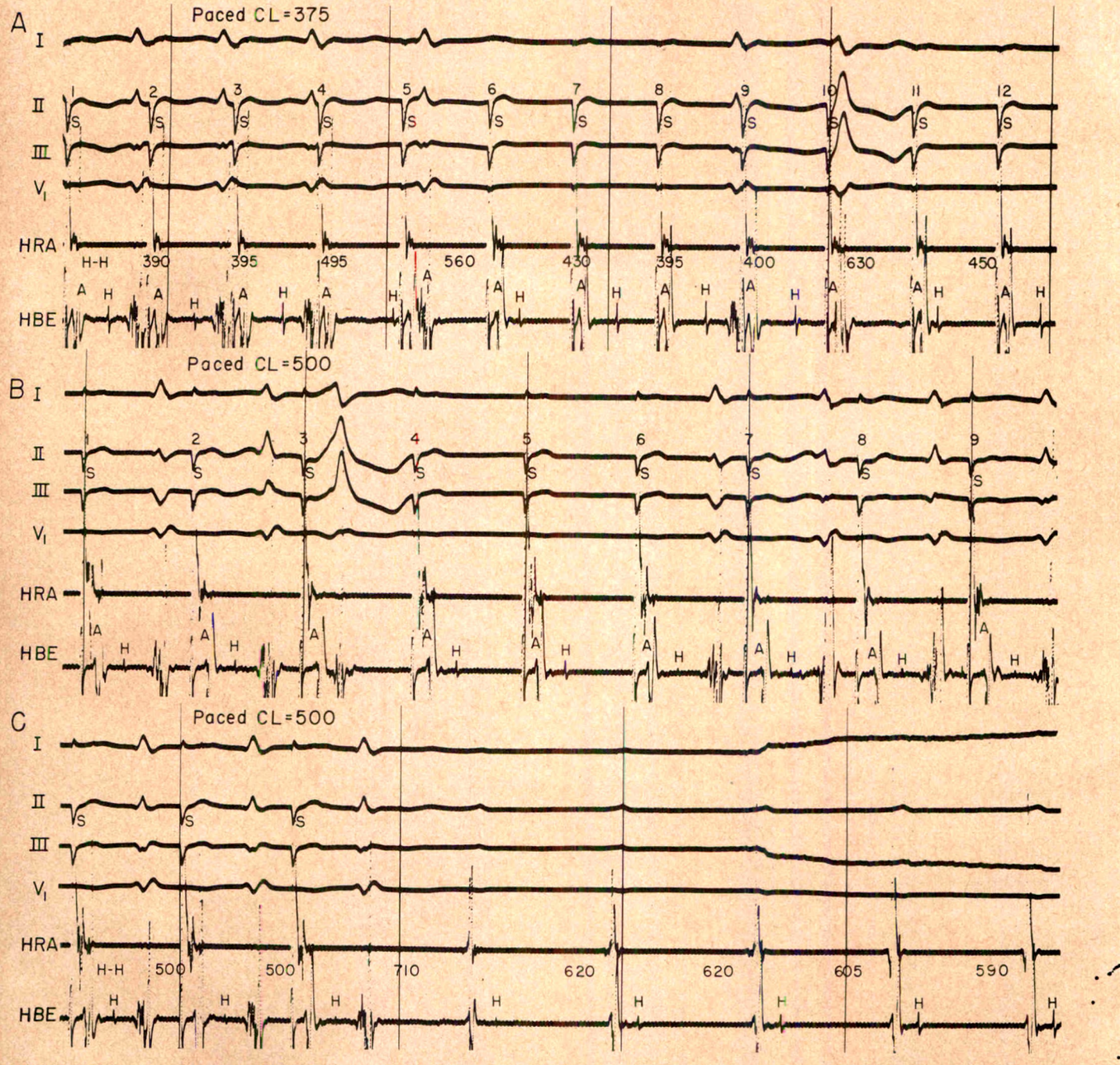

FIGURE 2. Recordings showing initiation of advanced second degree A-V block and paroxysmal A-V block during rapid atrial pacing and resumption of sustained A-V block after cessation of atrial pacing. **A,** initiation of advanced second degree A-V block during atrial pacing at a cycle length of 375 msec. Atrial paced beats 1, 2, 3, 4, 8 and 9 are conducted to the ventricles; beats 5, 6, 7, 11 and 12 are blocked. H-H intervals are listed. Wenckebach periodicity proximal to the H deflection occurred and, after completion of the Wenckebach sequence (beat 5), the H-H interval is 560 msec, and the subsequent 2 beats (beats 6 and 7) are blocked. The sequence repeats (beat 10), and advanced second degree A-V block results. Beat 9 is conducted with right bundle branch block and left posterior hemiblock. **B,** initiation of paroxysmal A-V block by a premature ventricular contraction during atrial pacing at a paced cycle length of 500 msec with 1:1 A-V conduction. See text for discussion. **C,** complete A-V block resumes after cessation of rapid atrial pacing. The first returning sinus beat has an H-H interval of 710 msec and is blocked. All subsequent sinus impulses have an H-H interval longer than 590 msec and are blocked. Abbreviations as in Figure 1.

conducted to the ventricles when the A_1-A_2 coupling interval was greater than 550 msec with an H_1-H_2 interval of greater than 550 msec. H_2 was always conducted to the ventricles when A_2 was coupled to the first sinus beat (A_1) after a ventricular escape beat at an A_1-A_2 coupling interval of less than 545 msec with an H_1-H_2 interval of less than 545 msec (Fig. 3, A to C and 4). The H_2-V_2 interval of the conducted beat progressively shortened from 290 to 70 msec as the H_1-H_2 interval decreased from 545 to 380 msec.

Atrial extrastimulus testing was also performed at an atrial driven cycle length of 500 msec (with 1:1 A-V conduction) (Fig. 5 and 6). As the A_1-A_2 interval was decreased from 500 to 350 msec, the H_1-H_2 interval decreased progressively, and H_2 was conducted to the ventricles with an H_2-V_2 interval of 70 msec (Fig. 6). As the A_1-A_2 interval was decreased further, the H_1-H_2 progressively lengthened because of A-V nodal relative refractoriness. H_2 was conducted to the ventricles when H_1-H_2 was less than 520 msec (Fig. 5, A and B, and 6). With a short A_1-A_2 coupling interval, H_2 was blocked distal to the His bundle recording site because of a long H_1-H_2 interval 540 msec) (Fig. 5C and 6). Although atrial extrastimulus testing was not performed at a coupling interval longer than A_1-A_1, the returning sinus beat during cessation of atrial pacing at a cycle length of 500 msec was always blocked distal to the His bundle recording site. The H-H interval of these beats always exceeded 550 msec (Fig. 6).

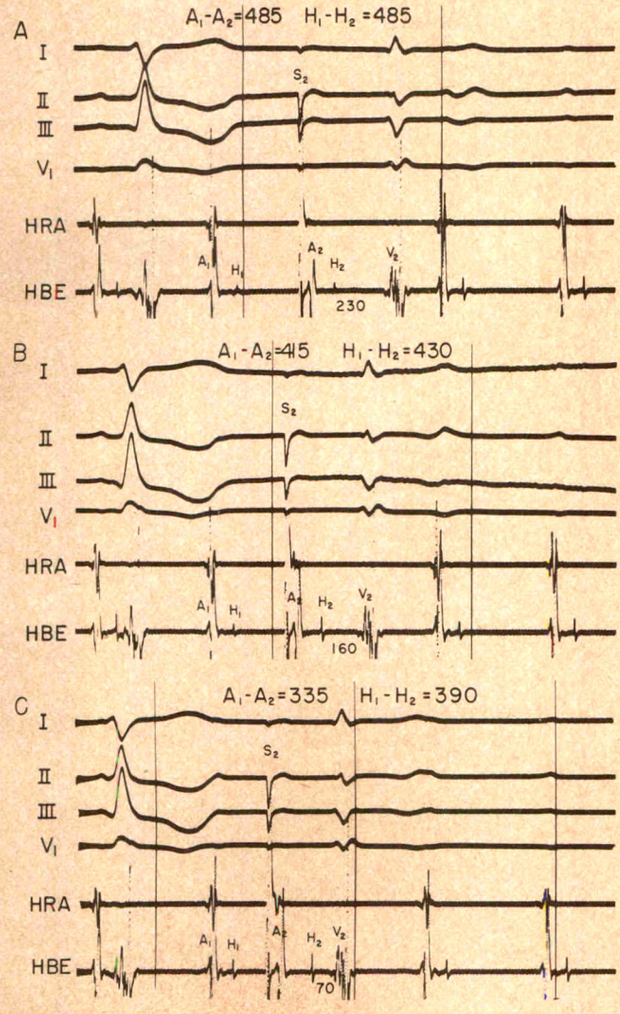

FIGURE 3. Recordings showing atrial extrastimulus testing coupled with sinus rhythm (cycle length 570 msec) with complete A-V block. A_1 and H_1 are, respectively, the atrial and His bundle responses to the sinus beat; A_2, H_2 and V_2 are the atrial, His bundle and ventricular responses to the extrastimulus (S_2). The A_1-A_2 and H_1-H_2 intervals are indicated at the top and the H_2-V_2 interval at the bottom of each panel. **A,** at an A_1-A_2 coupling interval of 485 msec, the H_1-H_2 interval is 485 msec, and H_2 is conducted to the ventricles with an H_2-V_2 interval of 230 msec. **B,** at an A_1-A_2 coupling interval of 415 msec, the H_1-H_2 interval is 430 msec, and H_2 is conducted to the ventricles with an H_2-V_2 interval of 160 msec. **C,** at an A_1-A_2 coupling interval of 335 msec, the H_1-H_2 interval is 390 msec, and H_2 is conducted to the ventricles with an H_2-V_2 interval of 70 msec. Abbreviations as in Figure 1.

Discussion

Genesis of bradycardia-dependent A-V block: The electrophysiologic mechanisms of bradycardia-dependent block have not been well defined. Singer et al.[13] demonstrated a voltage-dependent decrease of the rate of increase of action potential velocity (dV/dT) of the phase 0 and a decrease in action potential amplitude when hypopolarized canine Purkinje fibers were activated during spontaneous phase 4 depolarization. He also demonstrated a gradual shift of threshold potential toward 0 as phase 4 spontaneous depolarization progressed. The amplitude of action potential and dV/dT of phase 0 were totally voltage-dependent during both phase 3 repolarization and phase 4 depolarization. Extrapolating from these observations, Rosenbaum, Elizari and their co-workers[3,4,6,14,15] postulated that the hypopolarization of the resting membrane with enhanced phase 4 spontaneous depolarization was the

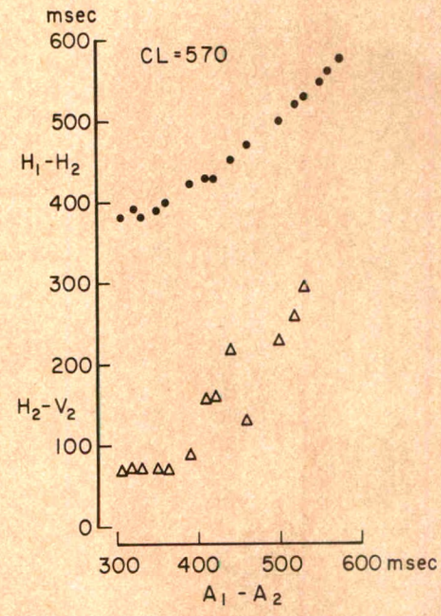

FIGURE 4. A_1-A_2, H_1-H_2 **(solid circles)** and A_1-A_2, H_2-V_2 **(open triangles)** curves during sinus rhythm with complete A-V block. At an A_1-A_2 interval of less than 545 msec, the H_1-H_2 interval is less than 545 msec and H_2 is conducted to the ventricles, at an A_1-A_2 interval of more than 550 msec, the H_1-H_2 interval is longer than 550 msec, and H_2 is blocked. The H_2-V_2 interval shortens progressively with shortening of the H_1-H_2 interval. CL = cycle length.

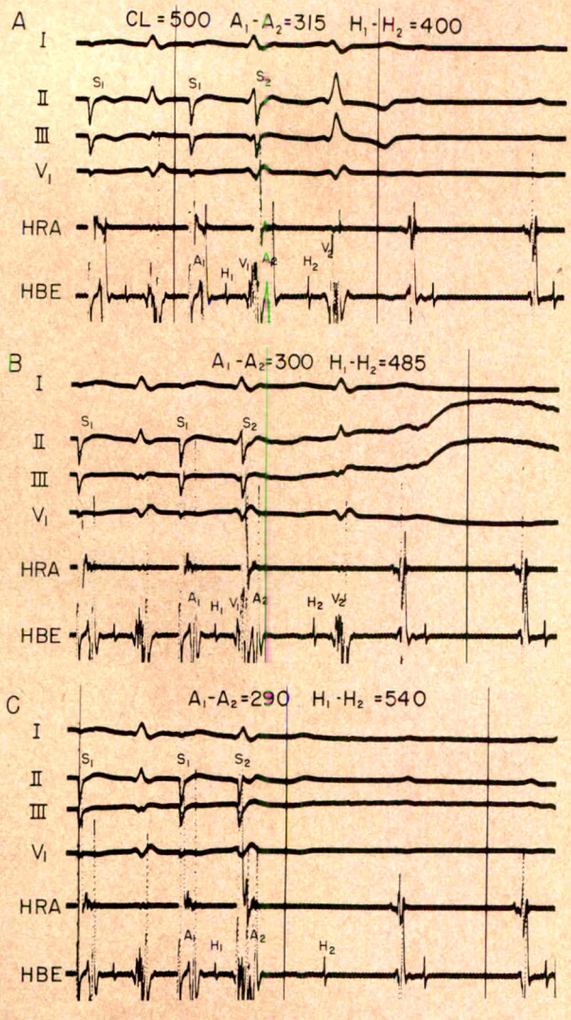

FIGURE 5. Recordings showing atrial extrastimulus testing coupled to an atrial driven cycle length of 500 msec with 1:1 A-V conduction. **A,** at an A_1-A_2 coupling interval of 315 msec, the H_1-H_2 interval is 400 msec, H_2 is conducted to the ventricles with an H_2-V_2 interval of 70 msec and a pattern of right bundle branch block with left posterior hemiblock. **B,** at an A_1-A_2 coupling interval of 300 msec, the H_1-H_2 interval is 485 msec, and H_2 is conducted to the ventricles with an H_2-V_2 interval of 70 msec. Left posterior hemiblock did not occur at this longer H_1-H_2 interval. **C,** at an A_1-A_2 interval of 290 msec, the H_1-H_2 interval lengthens to 540 msec, and H_2 is blocked. Abbreviations as in Figure 1.

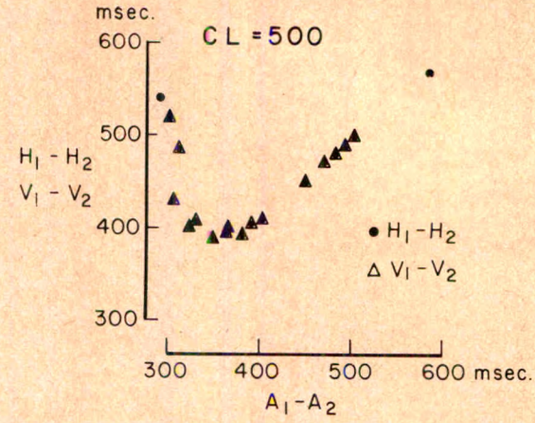

FIGURE 6. A_1-A_2, H_1-H_2 **(solid circles)** and A_1-A_2, V_1-V_2 **(open triangles)** curves at an atrial driven cycle length of 500 msec. Note that H_2 is conducted to the ventricles at an A_1-A_2 interval of 300 to 500 msec when the H_1-H_2 interval is shorter than 520 msec. The H_2-V_2 interval is 70 msec at all H_1-H_2 intervals; therefore, the V_1-V_2 interval is identical to the H_1-H_2 interval. At an H_1-H_2 interval longer than 540 msec, H_2 is not conducted to the ventricles. This occurs either with a short A_1-A_2 interval or with sinus returning beats at cessation of atrial pacing at a cycle length (CL) of 500 msec.

major factor facilitating clinically observed bradycardia-dependent block in the His-Purkinje system, whereas a prolonged refractory period of the action potential was responsible for tachycardia-dependent block. They termed the former "phase 4 block" and the latter "phase 3 block." In contrast, El-Sherif et al.,[16] on the basis of canine studies, suggested that a shift in threshold potential rather than enhanced phase 4 depolarization was the crucial factor in the genesis of bradycardia-dependent block. They also postulated a decrease in membrane responsiveness without marked enhancement of phase 4 depolarization as a contributing factor to the occurrence of bradycardia-dependent block.

In this study, we have described a patient who had bradycardia-dependent complete A-V block for 3 days. As in previous cases, the site of block was in the His-Purkinje system. Because the idioventricular escape rhythm had a configuration of right bundle branch block and right axis deviation, whereas the supraventricular conducted beats had a configuration of right bundle branch block with normal axis and occasional right or left axis deviation, the site of block was thought to be in the proximal bundle branch system. Because the block in the right bundle was probably established, the exact site of block could be in the proximal left bundle. The idioventricular rhythm probably originated from the left anterior fascicle, distal to the site of block. Sustained bradycardia-dependent complete A-V block lasting for 3 days has not previously been described. Our patient also demonstrated initiation of paroxysmal A-V block and development of advanced second degree A-V block during rapid atrial pacing with intact A-V conduction; these findings incorrectly suggested the occurrence of tachycardia-dependent block related to bradycardia-dependent block (see later).

Electrophysiologic observations during atrial extrastimulus testing: Atrial extrastimulus testing coupled with sinus rhythm with complete A-V block distal to the H deflection demonstrated that at critical H_1-H_2 intervals, H_2 was conducted to the ventricles and that the H_2-V_2 interval (very long at a long coupling interval) progressively shortened with shortening of H_1-H_2 coupling intervals. These findings strongly suggested that each sinus impulse penetrated to the site of

block, resetting a new state of membrane responsiveness. Membrane responsiveness of the conducting tissue at the site of block decreased progressively as the diastolic coupling interval (H_1-H_2) increased. When atrial extrastimulus testing was coupled with an atrial driven cycle length of 500 msec with intact A-V conduction, the conduction time of H_2 (H_2-V_2 interval) did not change with a change in the H_1-H_2 interval. However, H_2 was blocked at a critical long H_1-H_2 interval identical to the H_1-H_2 interval at which H_1 was not conducted to the ventricles during sinus rhythm. In other words, shortening of the driven atrial cycle length restored A-V conduction, eliminated bradycardia-related lengthening in conduction time but did not eliminate bradycardia-related block. The cell mechanisms underlying this observation are unclear but could relate to resting membrane potential, slope of diastolic depolarization and bradycardia-dependent decrease in membrane responsiveness.

A short episode of paroxysmal A-V block was precipitated by a premature ventricular beat occurring during intact A-V conduction (Fig. 2B). Activation from this premature beat apparently penetrated to the site of block (a concealed event, probably occurring during the ventricular electrogram). The next conducted beat (beat 4, Fig. 2B) thus had a diastolic interval longer than the critical interval allowing conduction and was blocked distal to the His bundle recording site. However, repetitive block of the subsequent impulses with resumption of conduction is difficult to explain.

Factors involved in initiation and sustaining of the A-V block: Rosenbaum et al.[3] postulated that once block was initiated, spontaneous phase 4 depolarization would progress to a critical state when conduction could no longer take place. They further postulated that unless an escape beat from the injured area or from another region could discharge the injured area, repolarizing the transmembrane potential to its maximal value, block would be repetitive. They observed that resumption of conduction occurred after an escape beat. In our patient, resumption of conduction did not occur during idioventricular escape rhythm. Furthermore, atrial extrastimulus testing during sinus rhythm with complete A-V block revealed that each sinus beat had penetrated to the injured area, resetting a new state of membrane responsiveness (see above). It appeared that the first blocked beat had created a state of maximal decrease in membrane responsiveness that gradually improved during the repetitive concealment of impulses with a cycle length of less than the critical diastolic interval until conduction was resumed. However, A-V block would sustain if the cycle length of the subsequent impulses were longer than the critical diastolic interval. Thus, once the block was initiated, the occurrence of a sustained or a paroxysmal block was partially dependent on the cycle length of the subsequent impulses. This hypothesis could also explain persistence of A-V block in the presence of idioventricular escape rhythm. Although the ventricular escape beat penetrated to the site of block and improved membrane responsiveness, it was not sufficient to allow conduction of the first sinus beat after the escape beat. However, this sinus beat would further improve membrane responsiveness, allowing conduction of subsequent supraventricular impulses arriving at cycle lengths of less than the critical diastolic interval (Fig. 3).

Effects of rapid atrial pacing—differentiation from tachycardia-dependent A-V block: Initiation of advanced second degree A-V block during rapid atrial pacing could be explained on a similar basis. During atrial paced A-V nodal Wenckebach periodicity, the H-H interval (between beats 4 and 6) encompassing the blocked P wave (beat 5) was longer than the critical interval, allowing conduction with resultant block of the latter H deflection (beat 6). This blocked beat created a state of decreased membrane responsiveness, resulting in repetitive block of beat 7 (paroxysmal A-V block). Because beat 7 arrived within the critical diastolic interval, it improved the membrane responsiveness, allowing conduction of the subsequent beats with an H-H interval shorter than the critical diastolic interval (beats 8 and 9). Perpetuation of Wenckebach periodicity associated with bradycardia-dependent paroxysmal A-V block produced a pattern of sustained advanced second degree A-V block. Without a His bundle recording, this type of block could be misinterpreted as "tachycardia-dependent block" or "phase 3 block." Because the block developed after a blocked P wave during Wenckebach periodicity, accurate diagnosis could be achieved with careful deductive analysis of the tracing. However, we can extend our observation and provide an alternative explanation for the "tachycardia-dependent block" frequently associated with the condition of bradycardia-dependent block. If second degree block occurred in the His-Purkinje system proximal to the area of bradycardia-dependent block, a pattern of advanced second degree A-V block could ensue without implying simultaneous occurrence of bradycardia- and tachycardia-dependent block in the same tissue.

In conclusion, we have demonstrated that bradycardia-dependent block can present with both sustained and paroxysmal A-V block. With bradycardia-dependent block, the nonconducted impulses penetrate to the site of block and reset the state of membrane responsiveness. The first blocked beat appeared to impose a state of maximal decrease in membrane responsiveness. Once a blocked beat was initiated, the occurrence of sustained or paroxysmal heart block was dependent on the cycle length of the subsequent beats. If the cycle length was longer than the critical diastolic interval, the block was sustained (sustained complete A-V block); if the cycle length was shorter than the critical diastolic interval, conduction resumed after a few beats (paroxysmal A-V block). Finally, we have also demonstrated that second degree tachycardia-dependent block occurring at a proximal site (A-V node) associated with bradycardia-dependent block at a distal site could produce advanced second degree A-V block. This was the mechanism of apparent tachycardia-dependent A-V block in our patient.

References

1. **Massumi RA:** Bradycardia-dependent bundle-branch block. Circulation 38:1066–1073, 1966
2. **Coumel P, Fabiato A, Waynberger M, et al:** Bradycardia-dependent atrioventricular block. J Electrocardiol 4:168–177, 1971
3. **Rosenbaum MB, Elizari MV, Lázzari JO, et al:** The mechanism of intermittent bundle branch block: relationship to prolonged recovery, hypopolarization and spontaneous diastolic depolarization. Chest 63:666–677, 1973
4. **Rosenbaum MB, Elizari MV, Levi RJ, et al:** Paroxysmal atrioventricular block related to hypopolarization and spontaneous diastolic depolarization. Chest 63:678–688, 1973
5. **El-Sherif N:** Tachycardia- and bradycardia-dependent bundle branch block after acute myocardial ischemia. Br Heart J 36: 291–301, 1974
6. **Corrado G, Levi RJ, Nau GJ, et al:** Paroxysmal atrioventricular block related to phase 4 bilateral bundle branch block. Am J Cardiol 33:553–556, 1974
7. **Castellanos A, Sung RJ, Cunha D, et al:** His bundle recordings in paroxysmal atrioventricular block produced by carotid sinus massage. Br Heart J 36:487–491, 1974
8. **Castellanos A, Khuddus SA, Sommer LS, et al:** His bundle recordings in bradycardia-dependent AV block induced by premature beats. Br Heart J 37:570–575, 1975
9. **Goodfriend MA, Barold SS:** Tachycardia-dependent and bradycardia-dependent Mobitz type II atrioventricular block within the bundle of His. Am J Cardiol 33:908–913, 1974
10. **Jonas EA, Kosowsky BD, Ramaswamy K:** Complete His-Purkinje block produced by carotid sinus massage. Circulation 50:192–197, 1974
11. **Scherlag BJ, Lau SH, Helfant RM, et al:** Catheter technique for recording His bundle activity in man. Circulation 39:13–18, 1969
12. **Denes P, Wu D, Dhingra R, et al:** The effects of cycle length in cardiac refractory periods in man. Circulation 49:32–41, 1974
13. **Singer DH, Lazzara R, Hoffman BF:** Interrelationships between automaticity and conduction in Purkinje fibers. Circ Res 21: 537–558, 1967
14. **Elizari MV, Nau GJ, Levi RJ, et al:** Experimental production of rate-dependent bundle branch block in the canine heart. Circ Res 34:730–741, 1974
15. **Rosenbaum MB, Elizari MV, Chiale P, et al:** Relationships between increased automaticity and depressed conduction in the main intraventricular conduction fascicles of the human and canine heart. Circulation 49:818–828, 1974
16. **El-Sherif N, Scherlag BJ, Lazzara R, et al:** Pathophysiology of tachycardia- and bradycardia-dependent block in the canine proximal His-Purkinje system after acute myocardial ischemia. Am J Cardiol 33:529–540, 1974

Electrophysiologic Effects of Acute Myocardial Infarction in Man

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Six patients undergoing surgery for ischemic heart disease were studied by means of epicardial electrodes affixed to the left ventricle. One patient who underwent triple coronary arterial bypass and plication of a left ventricular aneurysm had evidence of an acute myocardial infarction 1 day after operation. A surface electrocardiogram and a bipolar electrogram from the left ventricle were recorded before and after development of the infarction. The bipolar electrogram showed a marked loss of voltage and delay of conduction that were not present in the patients who underwent surgery but did not sustain an acute myocardial infarction. Thus, any acute myocardial infarction in conscious persons appears to be associated with areas of delayed epicardial action and diminution of local voltage. This observation suggests that the electrophysiologic mechanisms of infarction in man are similar to those of infarction in the dog.

Most of our knowledge about the mechanisms of ventricular arrhythmias in acute myocardial infarction is derived from studies in the canine heart.[1] In these studies, zones of infarction produced by coronary arterial ligation demonstrate slowing of conduction sufficient to permit the occurrence of reentrant arrhythmias.[2–4] The relevance of these studies to human myocardial infarction is unclear.[5] Precise electrophysiologic data on acute infarction in man, particularly in conscious patients, is difficult to obtain. In this study, we made serial electrophysiologic recordings from the hearts of six patients who underwent surgery for ischemic heart disease, including one who had an acute myocardial infarction 1 day postoperatively. The observations suggest that the electrophysiologic changes similar to those seen in experimental myocardial infarction occur in infarction in conscious man.

Methods

Six patients who underwent surgery for ischemic heart disease had bipolar electrodes for standby pacing placed on the left ventricle, in the distribution of the left anterior descending coronary artery. Bipolar electrograms were recorded from this electrode with an isolation unit on an Electronics for Medicine DR-8 research recorder with a filter frequency of 12 to 500 hertz at a paper speed of 100 mm/sec. All recordings were made with the patient supine. Conduction intervals were measured from the earliest onset of the QRS complex in three simultaneously recorded standard electrocardiographic leads to the major deflection of the bipolar electrogram recorded from the left ventricle. A Vernier measuring device, with an accuracy of ±1 msec at recorded paper speed, was used for measurements. Recordings were performed 4 to 5 hours postoperatively and then during the following 6 days.

Results

Control patients: Five patients underwent coronary bypass surgery with grafts to the left anterior descending coronary artery and had an uncomplicated postoperative course. In these patients, the local electrograms showed no change in conduction time and a mean decrease in voltage of 44.0 ± 11 percent from the

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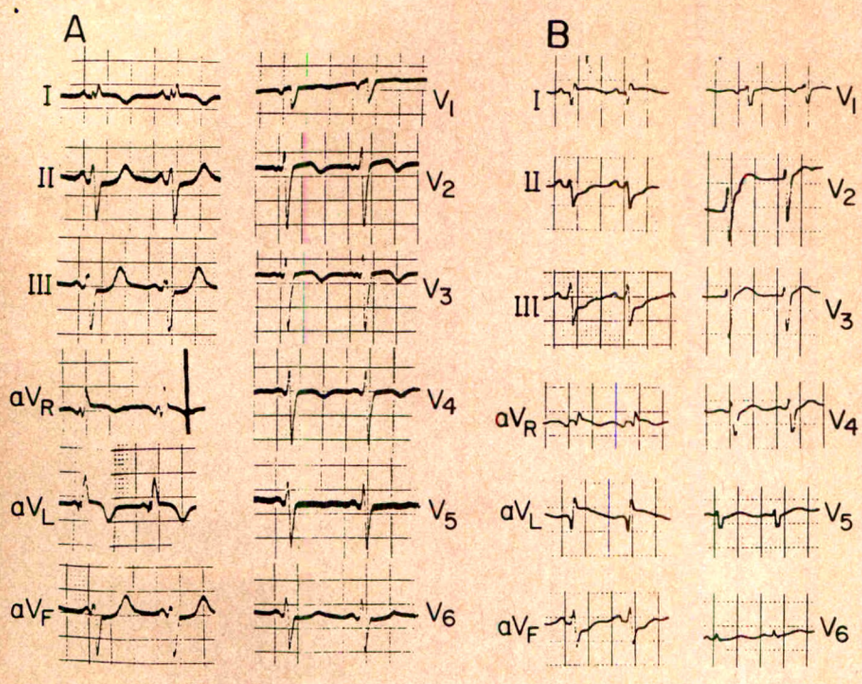

FIGURE 1. Twelve lead electrocardiograms. **A,** 4 hours postoperatively. The tracing is unchanged from the preoperative electrocardiogram. **B,** first postoperative day. Note new Q waves, S-T elevation and upright T waves in leads I and aVL and S-T depression in leads II, III and aVF.

first recording 4 hours postoperatively to the 6th postoperative day; these findings are similar to those reported by others.[6]

Electrophysiologic findings in a patient with acute myocardial infarction: The patient was a 42 year old woman with angina pectoris that was intractable despite pharmacologic therapy. Coronary arteriography revealed severe triple vessel disease with a Friesinger score of 13, relatively poor runoff and poor left ventricular function. At operation, diffuse scarring of the apicolateral area and a small apical aneurysm were noted. Three coronary bypass grafts, including one to the left anterior descending coronary artery, were constructed, and the apical aneurysm was plicated. During surgery, a bipolar electrode was placed on the left ventricle in an area adjacent to the middle third of the left anterior descending coronary artery. When cardiopulmonary bypass was discontinued, the patient's condition was hemodynamically unstable; an intraaortic balloon pump was inserted, and stable blood pressure and cardiac output were maintained.

The electrocardiogram 4 hours postoperatively (Fig. 1A) was unchanged from the preoperative tracing, and the bipolar electrogram recorded from the left ventricle (Fig. 2A) showed an amplitude of 2.7 mv and a conduction interval of 19 msec. The next morning (postoperative day 1), the patient became hypotensive while on the intraaortic balloon pump, and dopamine, 16 μg/kg/per min, was required to maintain a stable blood pressure and cardiac output. The surface electrocardiogram (Fig. 1B) showed new S-T elevation and new Q waves in leads I and aVL. The left ventricular electrogram (Fig. 2B) showed a 92 percent loss of voltage to 0.2 mv and an increase of the conduction interval to 28 msec. By postoperative day 2 administration of dopamine had been discontinued, but lidocaine therapy (2 mg/min) was started for ventricular arrhythmias. The electrocardiogram showed evolution of a lateral acute myocardial infarction, and local left ventricular activation time was further delayed to 33 msec (Fig. 1C). On day 3, both lidocaine therapy and the intraaortic balloon pump were discontinued. The electrocardiogram was unchanged, and the left ventricular electrogram (Fig. 1D) showed further delay in local activation to 36 msec. After this, the patient had no other complications. The left ventricular electrogram recorded 6 days postoperatively (Fig. 1E) showed a further decrease in voltage to 0.08 mv and shortening of the local conduction interval to 30 msec.

Discussion

Previous electrophysiologic studies on human myocardial infarction: Studies on intramyocardial conduction in man are difficult to perform.[7] Using epicardial mapping during open heart surgery, Daniel et al.[8] demonstrated delayed epicardial activation over zones of chronic infarction. Kaiser et al.,[9] using electrophysiologic mapping during open heart surgery, localized the infarct zone in a patient with acute myocardial infarction. Unipolar recordings revealed Q waves, and bipolar electrograms demonstrated low voltage and increased duration. Local activation time was not evaluated and, because no recordings were made before the development of infarction, change in local activation caused by the infarction could not be evaluated. Sung et al.[6] studied left ventricular bipolar electrograms in patients before and after coronary bypass surgery. In 13 of 19 patients, the voltage of the bipolar electrogram increased immediately after grafting. During the first 5 days postoperatively, the voltage of the electrogram decreased in 16 of 19 patients, with no change in local activation time. In our control patients, the first recordings were made several hours postoperatively, and the results were consistent with those of Sung et al.[6] In their study, three patients had a perioperative infarc-

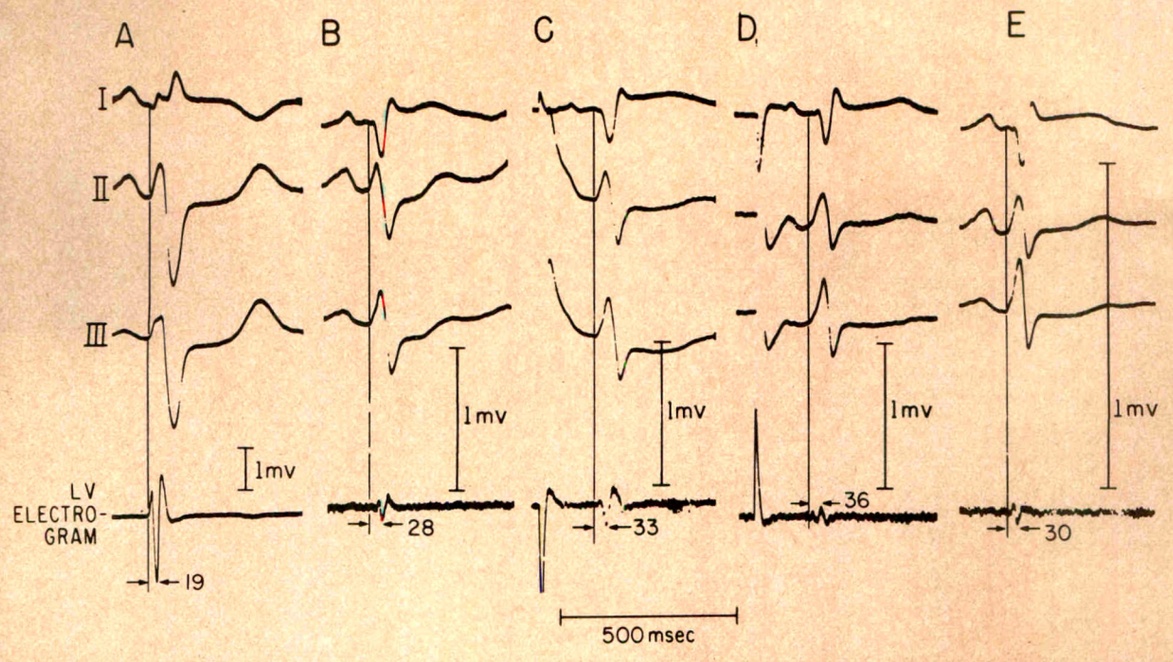

FIGURE 2. Standard electrocardiographic leads I, II and III with simultaneous bipolar electrogram recorded from the left ventricle (LV). **A,** 4 hours postoperatively, heart rate is 89 beats/min. Conduction interval from the onset of the QRS complex to the maximal deflection of the bipolar electrogram is 19 msec. Voltage of electrogram is 2.7 mv. **B,** first postoperative day. Note the new Q wave and S-T elevation in lead I. Heart rate is 120 beats/min. The conduction interval is 28 msec and voltage of the bipolar electrogram is 0.2 mv. **C,** second postoperative day. There is atrial pacing to a heart rate of 91 beats/min. The conduction interval is 33 msec, and voltage of the bipolar electrogram is 0.25 mv. **D,** third postoperative day. There is atrial pacing to a heart rate of 93 beats/min. The conduction interval is 36 msec, and voltage of the bipolar electrogram is 0.15 mv. **E,** sixth postoperative day. Heart rate is 103 beats/min. The conduction interval is 30 msec, and voltage of the bipolar electrogram is 0.08 mv.

tion, but their electrograms showed no change in conduction interval, and the changes in amplitude did not differ from those in patients without infarction. The authors attributed this finding to the fact that the electrodes did not lie in the zone of the infarction as predicted by the electrocardiogram.

Changes in left ventricular electrogram: Our patient clearly had an acute myocardial infarction on the first postoperative day. The left ventricular electrodes, which appeared to be in or near the infarct zone, demonstrated a marked loss of voltage and considerable slowing of activation. The further delay on day 2 may have been related to the evolution of the infarction, the withdrawal of dopamine or the administration of lidocaine.[10] The delay of activation on day 3 may have represented ischemia related to discontinuation of the intraaortic balloon pump. By day 6 voltage continued to decrease, but epicardial activation time, although still delayed, was shorter than previously. None of these changes occurred in our patients who underwent coronary bypass surgery but did not sustain infarction. Overall, the delay in activation and loss of voltage in the patient with acute infarction are similar to those occurring after ligation of a canine coronary artery.

Possible limitations of study: There are certain limitations to these observations. Only one patient with infarction was observed. Although postoperative myocardial infarction is not rare, the electrocardiographic changes of infarction are almost always present in the first electrocardiogram recorded in the recovery room.[11] It is thus quite unusual to be able to obtain a baseline electrogram after surgery but before the occurrence of infarction. The patient who had infarction also had plication of a left ventricular aneurysm. The control recording after surgery indicates that it is quite unlikely that the changes were secondary to plication of the aneurysm. Although dislodgment of the electrodes might explain our findings, this also appears unlikely because dislodgment was not seen in any of the control cases and would have had to occur precisely at the time of infarction. It is possible that the electrodes were located in the periinfarction zone rather than within the infarct itself. For clinical reasons, multiple interventions were often performed simultaneously. A change in heart rate occurred on day 2, but the changes in conduction interval persisted when the heart rate returned to baseline level. Although the total delay in epicardial activation was considerable, the delay demonstrated in these recordings did not extend beyond the refractory period of the ventricle and by itself would not be sufficient for reentry to occur (although our electrodes may not have been in the zone of maximal conduction delay).

Implications: Acute myocardial infarction in conscious persons appears to be associated with areas of delayed epicardial activation and diminution of local

voltage. As far as we know, this observation has not been made before, and it suggests that the electrophysiologic mechanisms of infarction in man are similar to those of infarction in the dog. This delay in epicardial activation may be important in the pathogenesis of reentrant ventricular arrhythmias.

References

1. **Wit AL, Bigger JT:** Possible electrophysiological mechanisms for lethal arrhythmias accompanying myocardial ischemia and infarction. Circulation 51, 52:Suppl III:III-96–III-115, 1975
2. **Waldo AL, Kaiser G:** A study of ventricular arrhythmias associated with acute myocardial infarction in the canine heart. Circulation 47:1222–1228, 1973
3. **Scherlag B, El-Sherif N, Hope R, et al:** Characterization and localization of ventricular arrhythmias resulting from myocardial ischemia and infarction. Circ Res 35:372–383, 1974
4. **Boineau JP, Cox JL:** Slow ventricular activation in acute myocardial infarction. A source of re-entrant premature ventricular contractions. Circulation 48:702–713, 1973
5. **Fozzard H:** Validity of myocardial infarction models. Circulation 51, 52:Suppl III:III-131–III-138, 1975
6. **Sung RJ, Bassett AL, Thurer RJ, et al:** Effects of coronary bypass surgery on the electrical activity of revascularized myocardium. J Thorac Cardiovasc Surg 73:269–277, 1977
7. **Kupersmith J:** Electrophysiologic mapping during open heart surgery. Prog Cardiovasc Dis 19:167–202, 1976
8. **Daniel T, Boineau J, Sabiston D:** Comparison of human ventricular activation with canine model in chronic myocardial infarction. Circulation 44:74–89, 1971
9. **Kaiser GA, Waldo AL, Bowman FO, et al:** The use of ventricular electrograms in operation for coronary artery disease and its complications. Ann Thorac Surg 10:153–162, 1970
10. **Kupersmith J, Antman E, Hoffman BF:** In vivo electrophysiologic effects of lidocaine in canine acute myocardial infarction. Circ Res 36:84–91, 1975
11. **Brewer D, Bilbro R, Bartel A:** Myocardial infarction as a complication of coronary bypass surgery. Circulation 47:58–64, 1973

Unusual Vasomotor Coronary Arterial Responses After Nitroglycerin

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Angiographic evidence of unusual vasomotor responses occurred in two patients after administration of sublingual nitroglycerin. In these patients, right coronary arterial segments that appeared angiographically normal before the administration of nitroglycerin showed narrowing after nitroglycerin. Adjacent segments in each of these vessels, as well as the other coronary arteries, dilated as expected. Both patients remained asymptomatic. Repeated administration of nitroglycerin did not alter the angiographic appearance of these vessels. No reason for the localized reduction of coronary arterial diameter was apparent. The possibility that nitroglycerin was associated with these unusual changes is an additional argument against the routine administration of nitrates before coronary arteriography.

Nitrates are known vasodilators and usually cause generalized coronary arterial dilation when administered before coronary angiography.[1,2] Recently, increased interest in coronary arterial spasm and its possible role in the pathophysiology of various ischemic syndromes has led some investigators to caution against the routine use of nitrates before angiography.[3,4] In addition, we previously suggested that use of nitroglycerin may result in angiographic overestimation of the degree of coronary stenosis.[2] This error is probably caused by nitroglycerin's potential to dilate the "normal" pre- and poststenotic segments to a greater degree than the stenotic region.

Recently, we observed two patients with unusual coronary angiographic responses after nitroglycerin. In each, localized arterial narrowing developed in the right coronary artery while the surrounding vessel and other coronary arteries dilated in the usual manner. These unexpected responses could not be explained by spontaneous or catheter-induced spasm or hemodynamic changes. These cases and the potential consequences of coronary narrowings that appear to be related to nitrates are briefly discussed.

Case Histories

Case 1

This 61 year old white man had had 12 years exertional and postprandial chest pain that was relieved with nitroglycerin. The resting electrocardiogram was normal. During pain induced with exercise stress, 2 mm S-T depression occurred in lead V_5 at 140 beats/min (stage III, Bruce protocol). Both the chest pain and the S-T depression persisted for 2 minutes after exercise. Cardiac catheterization studies, performed without premedication, revealed a left ventricular pressure of 130/18 mm Hg at rest. Cardiac output was preserved, and ventriculography showed minimal anterior wall hypokinesia.

Selective coronary arteriography performed with the Sones technique revealed significant coronary artery disease. There was proximal 70 percent narrowing of the diameter of the left anterior descending coronary artery and two diagonal branches. The circumflex obtuse marginal branch and posterior de-

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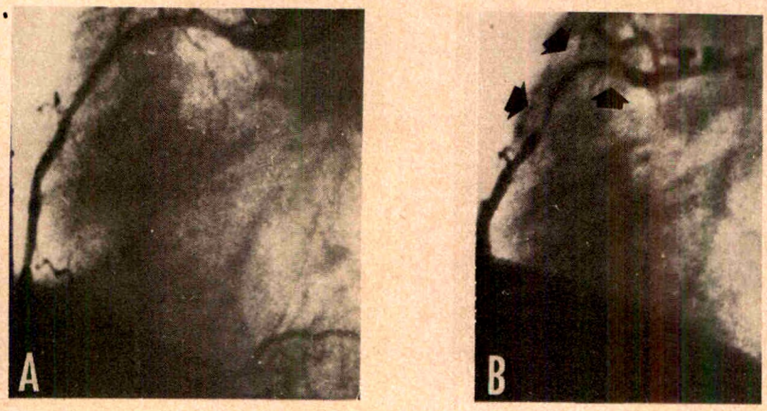

FIGURE 1. Case 1. Selected unretouched cineangiographic frames (left anterior oblique projection) of the right coronary artery before **(A)** and after **(B)** nitroglycerin (TNG). Note the long narrowed arterial segment after nitroglycerin **(arrows)** where only irregularity in luminal outline was noted before nitroglycerin. In **B** the most proximal segment engaged by the Sones catheter and the distal vessel dilated in the expected manner.

scending branch of the right coronary artery had 50 percent narrowings in their midportions. Multiple views of the right coronary artery revealed minimal irregularity of outline but no significant narrowing in the proximal segment. After the administration of 0.4 mg of sublingual nitroglycerin (Lilly, Indianapolis) there was no change in aortic pressure (130/70 mm Hg), heart rate (60 beats/min) or the multilead electrocardiogram. There was general dilation of the left coronary system with no major change of the narrowed segments. The proximal right coronary artery beyond the portion engaged with the Sones catheter (Fig. 1) had a long segment with a new 50 to 70 percent reduction in diameter, and adjoining vessel segments showed dilation. Despite removal of the catheter, a 20 minute wait and the sublingual administration of an additional 1.2 mg of nitrate, this unexpected vasomotor response persisted during multiple aortic cusp flushes. The patient did not experience chest pain at any time during cardiac catheterization.

Repeat coronary angiography on the following day revealed return of the narrowed segments to a normal diameter. At this time, 0.2 mg of ergonovine maleate (Lilly) was administered intravenously in an attempt to provoke coronary arterial spasm. No symptoms developed, and there were no significant angiographic or electrocardiographic changes. Subsequent administration of nitroglycerin showed the expected generalized dilatory response in the right coronary artery. During a follow-up period of 21 months, the patient has done well on medical therapy that includes nitrates.

Case 2

This 53 year old white man had had for 6 months sharp chest pain unrelated to exertion with an inconsisent response to nitrates. The resting electrocardiogram was normal and did not change during pain. Cardiac catheterization studies performed without premedication disclosed normal resting hemodynamic measurements; the left ventriculogram was normal. Selective coronary arteriography performed with the Sones technique revealed normal findings and an anatomically dominant right coronary artery. After administration of 0.4 mg of sublingual nitroglycerin, aortic pressure changed from 130/60 to 120/80 mm Hg and heart rate increased from 57 to 70 beats/min. A 12 lead electrocardiogram was unchanged. Repeat coronary arteriography revealed generalized dilation of the left coronary arterial system. Two proximal right coronary arterial segments had narrowings of 90 percent of diameter (Fig. 2), and the segments between and distal to these new narrowings were dilated. The new narrowings persisted for at least 20 minutes despite repeated sublingual administration of nitroglycerin tablets to a total dose of 1.2 mg. The patient did not experience chest pain at any time during cardiac catheterization. At a later date, intravenous administration of 0.2 mg ergonovine failed to produce chest pain or electrocardiographic changes. Coronary angiography was not repeated after the administration of ergonovine. During a follow-up period of 9 months the patient's condition has remained stable with no cardiac medication.

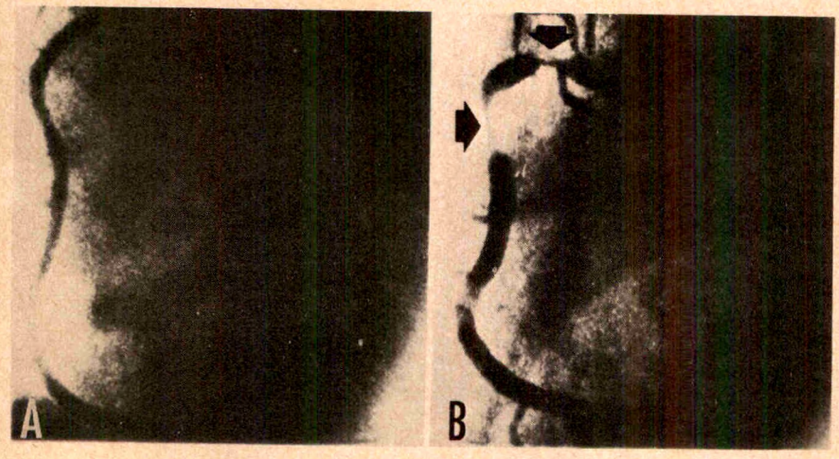

FIGURE 2. Case 2. Selected cineangiographic frames (left anterior oblique projection) of the right coronary artery before **(A)** and after **(B)** nitroglycerin (TNG). Note the multiple narrowed arterial segments **(arrows)** after nitroglycerin; the artery was normal in **A.** As in Case 1, after nitroglycerin the most proximal segment engaged by the Sones catheter and the distal vessel dilated in the expected manner.

Discussion

Vasomotor changes producing discrete coronary arterial narrowing, such as those we observed after administration of sublingual nitroglycerin, have not previously been reported. Although these new narrowed segments appeared after the administration of nitroglycerin, this temporal relation does not prove that they were produced by nitroglycerin. However, the lack of other reasonable explanations suggests that nitroglycerin influenced these vasomotor responses.

Possibility of catheter-induced coronary narrowing: This possibility deserves comment. Both spontaneous narrowing and mechanically induced coronary narrowing appear to occur more commonly in the right than in the left coronary artery.[1] Dynamic narrowing induced by a catheter or injection of contrast medium usually occurs at the site of the catheter tip in the proximal part of the coronary artery and is reversed with nitroglycerin.[1] The narrowings we observed after nitroglycerin occurred some distance from the catheter tip, and there was dilation of the most proximal coronary segments, which were in contact with the Sones catheter tip. In our opinion, this is an unusual location for mechanically induced spasm. Because catheter-induced spasm was considered at the time of catheterization, attempts were made to reverse these vasomotor changes. Sinus of Valsalva flushes without catheter engagement in the right coronary ostium after additional nitrate administration and waiting periods of up to 20 minutes did not alter the new narrowed segments. Although these vasomotor changes were observed for a relatively long period, it is possible that they represent delayed resolution of catheter-induced spasm. If they do, it seems necessary to postulate that nitroglycerin sensitized some arterial segments to catheter stimulation while dilating adjacent segments in an expected manner. It is reasonable to question the potency of the nitroglycerin in these cases. The dilatory response of the surrounding arterial segments and other coronary arteries indicates that these particular nitroglycerin tablets, which were from different bottles, were potent. Additionally, the modest change in aortic pressure in Case 2 and the lack of change in Case 1 after nitroglycerin are not likely to account for our observation.

Nitroglycerin-induced versus spontaneous spasm of variant angina: That the alterations in coronary tone were transient is suggested first by the return to normal at restudy the following day in Case 1, and by the benign follow-up clinical course of both patients. Neither patient had or has subsequently experienced the clinical syndrome of variant angina or infarction. Subsequent challenge with ergonovine maleate failed to produce chest pain or electrocardiographic changes in either patient. Thus, spontaneous spasm of the type seen in variant angina is unlikely.[5,6] Patient 1 had coronary artery disease and angina on effort, and during the follow-up period continued to respond well to nitroglycerin.

Potential dangers: This unexpected angiographic evidence of coronary arterial narrowing after nitroglycerin indicates a potential danger. First, because nitrates usually decrease blood pressure and increase heart rate, extreme hemodynamic changes[7] or the development of more significant narrowings theoretically could lead to myocardial ischemia. Perhaps the hypotension and bradycardia observed after nitroglycerin in the setting of acute myocardial infarction[7] were unrecognized instances of right coronary arterial spasm. Additional nitroglycerin did not reverse the narrowings, and is thus probably not a beneficial therapy. Also of concern is the possibility that surgical revascularization might have been prescribed for nonfixed narrowings such as these. Initial routine administration of nitroglycerin before coronary arteriography in these cases might have led to the incorrect diagnosis of severe disease, whereas it is apparent that significant fixed stenosis is not present in either of these right coronary arteries.

We have no explanation for these coronary vasomotor changes. The possibility of observing such changes after nitroglycerin adds to the argument against the routine administration of nitrates before coronary angiography.[2]

References

1. **Gensini GG:** Coronary Arteriography. New York, Futura Publishing, 1975, p 420–435
2. **Feldman RL, Pepine CJ, Curry RC, et al:** A case against the routine use of nitroglycerin prior to coronary angiography. Br Heart J, in press
3. **Chahine RA, Luchi RJ:** Coronary arterial spasm: culprit or bystander. Am J Cardiol 37:936–937, 1976
4. **Bennett KR:** Coronary artery spasm: the effect of cardiovascular laboratory premedication practice. Cath Cardiovasc Diag 2:321–327, 1976
5. **Curry RC, Pepine CJ, Sabom MB, et al:** Effects of ergonovine in patients with and without coronary artery disease. Circulation 56: 803–809, 1977
6. **Weiner L, Kasparian H, Duca PR, et al:** Spectrum of coronary arterial spasm. Clinical, angiographic and myocardial metabolic experience in 29 cases. Am J Cardiol 33:945–955, 1976
7. **Come PC, Pitt B:** Nitroglycerin-induced severe hypotension and bradycardia in patients with acute myocardial infarction. Circulation 54:624–628, 1976

Remission of Angina Pectoris*

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A report from the Framingham Study in a recent issue of the Journal[1] suggests that angina pectoris need not always progress inexorably to coronary death but may, at times, completely disappear. Kannel and Sorlie[1] found that one third of a group of patients reporting substernal distress on a routine examination were asymptomatic when reevaluated 2 years later. Because only 1 of the 61 patients with transient angina died during the 4 subsequent years of observation, it seems fair to ask whether they did indeed have coronary artery disease.

Relation of Angina Pectoris and Coronary Artery Disease

The question of the relation between angina pectoris and coronary artery disease is not new. Edward Earl of Clarendon (1660), Morgagni (1707) and Heberden (1768) all described the symptom complex studied in Framingham, although it was Jenner who first proposed that coronary arterial sclerosis leads to angina pectoris.[2,3] This view was widely disputed, and in 1854 Stokes[4] wrote that "... coronary obstruction is probably not infrequent; but as a cause of angina, its action is remote and its existence unnecessary."

Osler[5] devoted his three Lumleian Lectures in 1910 to angina pectoris, a subject he noted to be "full of knotty problems which lend themselves to speculation." He believed that angina pectoris was closely related to coronary artery disease but emphasized the wide range of symptoms "from the trifling sense of substernal distress to the vascular ictus by which a man is felled as with a club." Sir William, after observing that 33 of his 268 patients were physicians, went on to classify their condition into three categories: formes frustes, mild and severe. Forty-three patients were considered to have mild angina and had long periods in which they were without pain. As in the group reported on in the Framingham study, more than half of these 43 patients were women.

Thirty years later, Blumgart et al.[6] presented definitive evidence that angina pectoris was almost always associated with severe coronary artery disease. Injecting radiopaque medium into the coronary arteries during postmortem examination, they found that the hearts of patients with angina usually showed one or more occlusions of coronary arteries with a rich development of collateral circulation. Subsequent postmortem studies have emphasized that severe coronary arterial occlusive disease can be expressed as angina pectoris, acute myocardial infarction, congestive heart failure or sudden ischemic death. The type of clinical expression does not seem to be related to the severity of coronary artery disease because Roberts[7] has shown a similar degree of luminal obliteration in patients with isolated angina pectoris or ischemic heart failure without pain.

Angina Pectoris As an Indicator of Coronary Artery Disease

How sensitive is angina pectoris as a diagnostic indicator of coronary artery disease? Allison et al.[8] found evidence of coronary artery disease in 82 percent of 430 unselected patients subjected to autopsy at the Boston City Hospital; the disease was severe in 43 percent. Only 19 percent of the patients with severe disease had had angina, and the number of occlusions was identical in the patients with and without angina. Spiekerman et al.[9] took advantage of the high autopsy rate in Rochester, Minnesota for both hospital and out of hospital deaths and found evidence of coronary artery disease in 74 percent of all postmortem examinations. Careful clinical study revealed that only 32 percent of persons who died of coronary artery disease had experienced angina.

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Specificity, the percent of true negatives, can also be estimated from these two studies. Allison et al.[8] noted that only 1 of 130 persons with little or no coronary disease experienced symptoms suggesting angina pectoris; almost all of the patients noted by Spiekerman et al.[9] to have angina pectoris exhibited severe coronary artery disease. Nevertheless, it must be remembered that angina is a symptom and can occur in the presence of normal coronary arteries in patients with anemia, aortic stenosis, obstructive cardiomyopathy or other conditions.

Coronary arteriography permits another assessment of the specificity of angina pectoris. Proudfit et al.,[10] analyzing the extensive Cleveland Clinic experience, found that 94 percent of patients with "typical" angina and 65 percent of those with atypical angina had significant coronary artery disease; 96 percent of those thought to be normal and 81 percent of those listed as probably normal had relatively normal coronary arteries. Thus, angina is present in less than one third of patients with severe coronary artery disease; however, when present, it is a reliable indicator of disease.

What is the cause for chest pain in those 61 patients reported by Kannel and Sorlie[1] to have typical anginal symptoms initially but not on subsequent follow-up studies? Presumably at least 80 percent of these patients had coronary artery disease. Angina pectoris is not a trivial symptom but implies myocardial ischemia and the possibility of sudden death. The studies performed by Katz et al.[11] 40 years ago suggested that angina might be caused by a diffusible acid substance arising from ischemic tissue. More recent evidence suggests that ischemic tissue liberates a variety of substances that stimulate small unmyelinated fibers within the myocardium sending back impulses to the spinal cord and higher centers. Some of this neural traffic spreads out within the spinal cord and leads to pain and hyperesthesia in adjacent dermatomes; other impulses reach higher integrating centers and evoke a sympathetic response characterized by tachycardia, sweating, vasoconstriction, anxiety and a sensation of "impending dissolution."

Implications of the Framingham Study

The report from Framingham emphasizes the strengths and weaknesses of epidemiologic study. The notion of mild and transient angina—an idea dating at least from Osler—has been confirmed; this promising lead should now be vigorously explored. If these patients really have coronary artery disease, why the surprisingly good prognosis? It would be of great interest to know whether they have less luminal obliteration than those with stable angina pectoris and whether they would manifest S-T segment abnormalities or regional hypoperfusion during vigorous exercise. Perhaps these patients have nonocclusive atheromatous plaques that occasionally trigger platelet aggregation and initiate a small thrombus that shortly disappears. Or perhaps the stress of everyday life, together with the catecholamine release related to cigarette smoking, leads to transient increases in myocardial oxygen requirements that cannot be met by a modestly diseased vascular bed. Osler[5] suggested that "there may be a perverted internal secretion which favors spasm of the arteries," and this could turn out to be norepinephrine or thromboxane A_2. At any rate, continuing evaluation of this unusual group could shed additional light on the progression of ischemic heart disease, particularly if epidemiologic observation is buttressed by detailed physiologic study.

References

1. **Kannel WB, Sorlie PD:** Remission of clinical angina pectoris: the Framingham Study. Am J Cardiol 42:119–123, 1978
2. **Willius FA, Keys TE:** Cardiac Classics. St Louis, MO, CV Mosby, 1941, p 217–224
3. **Mason RH:** Classic Descriptions of Disease, third edition. Springfield, IL, Charles C Thomas, 1945, p 416–422
4. **Stokes W:** The Diseases of the Heart and the Aorta. Dublin, Hodges, Smith, 1854
5. **Osler W:** The Lumleian lectures on angina pectoris. Lancet 1: 697–702, 839–844, 973–977, 1910
6. **Blumgart HL, Schlesinger MJ, Zoll PM:** Angina pectoris, coronary occlusions and collateral circulation. JAMA 116:9–97, 1941
7. **Roberts WC:** The coronary arteries and left ventricle in clinically isolated angina pectoris. Circulation 54:388–390, 1976
8. **Allison RB, Rodriguez FL, Higgins EA Jr, et al:** Clinicopathologic correlations in coronary atherosclerosis. Four hundred thirty patients studied with postmortem coronary angiography. Circulation 27:170–184, 1963
9. **Spiekerman RE, Brandenburg JT, Achor RWP, et al:** The spectrum of coronary heart disease in a community of 30,000. A clinicopathologic study. Circulation 25:57–65, 1962
10. **Proudfit WL, Shirey EK, Sheldon WC, et al:** Certain clinical characteristics correlated with extent of obstructive lesions demonstrated by selective cine-coronary arteriography. Circulation 38:947–954, 1968
11. **Katz LN, Lindner E, Landt H:** On the nature of the substance(s) producing pain in contracting skeletal muscle; its bearing on the problems of angina pectoris and intermittent claudication. J Clin Invest 14:807–821, 1935

EXERCISE TESTING IN CHRONIC STABLE INFERIOR MYOCARDIAL INFARCTION

Several additional aspects of the performance of exercise testing in patients with chronic stable inferior myocardial infarction should be mentioned in relation to the article by Miller et al.[1]

1. Only a three lead system, comprising leads I, aVF and V_5 was used, whereas Sheffield et al.[2] have indicated that at least six different leads are required to detect all the instances of exertional S-T segment depression that can be registered in a conventional 12 lead electrocardiogram.

2. The use of a single variable such as the S-T segment to determine the positivity or negativity of an exercise test without using signs, symptoms, general appearance of the patient, blood pressure responses, heart rate responses and the use of appropriate isotopes, represents a "regressive position." [3] Clinical symptoms such as shortness of breath, chest pain, chest pressure, chest discomfort or other anginal equivalents including subscapular pain and throat discomfort, for example, should also be used in the overall evaluation of the positivity or negativity of an exercise test.

3. Because the patients were known to have coronary artery disease, fluoroscopic examination for calcium would have been a simple noninvasive tool to help in the evaluation of the major left coronary arteries. The finding of calcification in the area of the left anterior descending coronary artery, circumflex or left main coronary artery, although not 100 percent diagnostic, would at least alert the physician as to the possibility and probability of left coronary artery disease. This may then help identify the subset of patients who are at greatest risk of sudden death or subsequent myocardial infarction.

4. The use of echocardiography may also be of value in defining the motion of the ventricular system and the possibility of left coronary artery disease.[4]

The realization that one can anticipate a 5 year mortality rate of 50 to 75 percent for nearly two thirds of all patients with isolated inferior infarction certainly elucidates the importance of defining the severity of the coronary artery disease in these patients. With use of the exercise evaluation and all the variables mentioned, the noninvasive clinical data may be better predictors than Miller indicates. I am not decrying the use of angiography to define coronary arterial pathoanatomy; however, use of these noninvasive methods to select the subset with the greatest risk of disease of the left coronary arterial system would place less burden on the angiographers who must perform these procedures and, at the same time, justify the minor risk and the psychosocial and economic impact of the procedure. Should the emphasis be placed on noninvasive procedures, we may eventually be fortunate enough to identify those persons at high risk whose coronary pathologic anatomy could be defined and appropriate measures taken to increase both the quality and quantity of life.

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References

1. **Miller RR, DeMaria AN, Vismara LA, et al:** Chronic stable inferior myocardial infarction: unsuspected harbinger of high-risk proximal left coronary arterial obstruction amenable to surgical revascularization. Am J Cardiol 39:954–960, 1977
2. **Sheffield LT, Reeves TJ, Blackburn H, et al:** The exercise test in perspective. Circulation 55: 681–682, 1977
3. **Liss JP:** Exercise testing and arteriography. Am J Cardiol 40:142, 1977
4. **Joffe CD, Brik H , Teichholz LE, et al:** Echocardiographic diagnoses of left anterior descending coronary artery disease. Am J Cardiol 40:11–16, 1977

REPLY

Improved noninvasive techniques are needed to define the high risk subgroup of patients with inferior myocardial infarction that we recently described. Unfortunately, the available techniques are not sufficiently sensitive to define all patients with the common circumstance of severe right coronary disease (responsible for the inferior myocardial infarction) and associated lesions of the left anterior descending or circumflex coronary artery, or both. Single lead electrocardiography during exercise is inadequate. However, Ellestad[1] has stated that virtually all S-T segment information is found in leads II, aVF and V_3 to V_6. Further, Froelicher et al.[2] have suggested that leads V_4 and V_6 are not abnormal in the presence of a normal lead V_5 or CC_5 and, further, that visual interpretation indicates close agreement between precordial lead V_5 and bipolar lead CC_5, whereas bipolar lead CM_5 appears to be less sensitive than either V_5 or CC_5. In contrast, Blackburn et al.[3] found lead CM_5 to be most sensitive. Thus, there is considerable controversy concerning the optimal lead system and furthermore, although computerized evaluation of S-T segment slopes from multiple bipolar and conventional leads may ultimately provide the most specific and sensitive assessment of electrocardiographic stress response, there are considerable data to support the use of a multiple lead system that includes an inferior lead and lead V_5.

We agree that all available clinical criteria in addition to S-T alterations should be utilized in assessing the response to exercise. However, the occurrence of angina is clearly a subjective event, and the presence of exercise-induced chest pain in patients with prior inferior myocardial infarction and occlusive disease of either the right coronary artery or the circumflex coronary arterial system may be nonspecific relative to additional anterior or lateral wall ischemia consequent to left anterior descending coronary artery disease. The important question is: Does the absence of exercise-induced chest pain in the presence of an inferior myocardial infarction rule out additional significant disease of the left coronary arterial system?

Our recent findings[4] indicate that 47 percent of patients with documented two vessel coronary disease and 23 percent of patients with documented three vessel disease may have no exercise-induced chest pain. Additionally, the heart rate-blood pressure product obtained at maximal exercise in patients with documented disease of both the left anterior descending and right coronary arteries was not significantly different from that of patients with disease confined to the right coronary artery.[4]

The finding of calcification in the area of the proximal left coronary artery should alert the physician to the possibility of left coronary artery disease. However, in our relatively young patients (mean age 52 years) the absence of left coro-

nary arterial calcification is certainly a nonspecific finding. Moreover, although coronary arterial calcification indicates disease of the vessel wall, it does not always indicate important stenotic lesions.

Finally, concerning the use of echocardiography to identify abnormal septal motion that may serve as a marker of left anterior descending coronary disease, Gordon and Kerber[5] recently suggested that abnormal septal motion in patients with coronary disease and no other cause for abnormal septal motion is relatively specific for lesions of the left anterior descending coronary artery. However, the technique is quite insensitive because 54 percent of patients with such lesions have normal septal motion.

In conclusion, continued efforts should be made to improve the specificity and sensitivity of noninvasive means of identifying patients at high risk for accelerated mortality related to coronary disease. The great advances in the resting and exercise thallium-201 myocardial perfusion scans may afford a means of identifying the high risk subgroup of patients who have prior inferior myocardial infarction and, in addition, have stenosis of the proximal left coronary arteries.

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References

1. **Ellestad MH:** Stress Testing. FA Davis, Philadelphia, 1975
2. **Froelicher VF Jr, Wolthius R, Keiser N, et al:** A comparison of two bipolar exercise electrocardiographic leads to lead V_5. Chest 70:611, 1976
3. **Blackburn H, Taylor H, Okamoto N, et al:** A systematic comparison of chest lead configurations employed for monitoring during exercise. In, Physical Activity and the Heart. Springfield, IL, Charles C Thomas, 1967
4. **Tonkon MJ, Miller RR, DeMaria AN, et al:** Multifactor evaluation of the determinants of ischemic electrocardiographic response to maximal treadmill stress testing in coronary disease. Am J Med 62:339–346, 1977
5. **Gordon MJ, Kerber RE:** Interventricular septal motion in patients with proximal and distal left anterior descending coronary artery lesions. Circulation 55:338–340, 1977

DELAYED RETURN OF ELECTROCARDIOGRAPHIC TRACING AFTER DEFIBRILLATORY ELECTRIC SHOCK CAUSED BY ELECTROCARDIOGRAPHIC MONITOR/ELECTRODE INCOMPATIBILITIES

A very subtle and serious hazard is present when certain types of monitoring electrodes are used with certain types of electrocardiographic monitors and recorders. The consequence occurs immediately after defibrillation or cardioversion and appears as one or more effects: (1) excessive delay of return of the electrocardiographic tracing to the monitor screen or recorder; (2) loss of the electrocardiographic signal from the tracing with the latter erroneously appearing as a straight line; and (3) distorted or reduced size of the electrocardiographic tracing. These effects occur when the monitor and electrodes are incompatible with each other. They may also occur with monitoring methods that monitor through the paddles, appearing when the electrode paste, paddle metal and the monitor are incompatible. Not all manufacturers of monitors, recorders and electrodes are fully aware of these incompatibilities; thus, use of their product with other products they may recommend does not necessarily assure compatibility.

Monitoring electrodes: During an electric defibrillatory shock, a portion of the electric current flows through the patient monitoring electrodes and causes electrochemical reactions within the electrodes. These reactions charge the electrodes, much as a battery is charged, and produce in the electrodes small voltages that persist after defibrillation. These voltages and the electrocardiographic voltage are received by the monitor. Although the monitor displays only the electrocardiogram, the monitor must be capable of handling the electrode voltages. If the electrode voltages are larger than this capability, the monitor cannot function properly and the electrocardiographic signal is distorted or blocked. The electrical input resistance of the monitor drains charge from the electrodes, gradually reducing their voltages. For the period that the electrode voltages are in excess of the capability of the monitor, the monitor does not operate properly.

Monitoring "through the paddles": An analogous situation occurs with some monitoring systems that monitor "through the paddles." During an electric defibrillatory shock, the electric current causes electrochemical reactions and small electrode voltages in the paddle-paste interfaces. Immediately after the shock, the paddles are switched to connect them to the monitor, and the electrode voltages, combined with the electrocardiogram, are received by the monitor.

Electrode voltage characteristics: The quantity of charge accumulated within an electrode and its resultant voltage are determined chiefly by the composition of the electrode. The rate at which the charge is dissipated depends on the electrode composition and the input resistance of the monitor. Some electrodes produce voltages that persist above 400 mv for more than 30 seconds when used with monitors having typical input resistance levels. Others decrease to less than 100 mv in 5 seconds. Various brands and models of monitors and recorders have different capabilities for handling the electrode voltages. Some may function well with up to 1,000 mv, but others cannot function with more than 140 mv. Whenever high millivoltage electrodes are used with monitors having low millivoltage capabilities, a prolonged loss of the electrocardiogram may be expected.

No single specification of a monitor uniquely indicates the capability of a monitor to tolerate the electrode voltages, but for most monitors the "maximal differential direct current offset voltage" is the limiting characteristic; electrode voltages in excess of this maximum will interfere with function. If this specification is not given in the operator's manual, it can usually be obtained from the manufacturer. Electrode manufacturers do not generally publish electrode voltage characteristics, but such information may be available upon request.

Recommendations: (1) Medical organizations experiencing these problems should consider seeking alternate types of electrodes known to have low electrode voltages after defibrillatory shocks. (2) Equipment specifications should be checked or measured to identify monitors that are compatible only with certain electrodes. Some operator's manuals may indicate electrode requirements. (3) Some electrode manufacturers produce two grades of electrodes that are similar in appearance and packaging. New shipments should always be carefully checked.

Finally, certain monitors and recorders have selectable filter settings for "monitor" and "diagnostic" modes. The "monitor" setting should be used during defibrillatory procedures because this setting permits more rapid compensation for electrode voltages when the voltages are within the normal operating range of the monitor or recorder. Recorders having only diagnostic filter characteristics are usually not ideal for defibrillatory procedures.

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ATROPINE AND SINUS NODAL RECOVERY TIME

The excellent article by Reiffel et al.[1] very clearly underlines the difficulty of attaining simultaneous high sensitivity and specificity in the assessment of sinus nodal dysfunction. We also have been convinced of the utility of combining Holter electrocardiographic recording with functional testing. Moreover, we recently started plotting the value of sinus nodal recovery time on the regression equation proposed by Scheinman et al.[2] in an effort to improve the accuracy of the classic corrected sinus nodal recovery time. In addition, we now systematically submit every patient studied for possible sinus nodal dysfunction to the atropine test, including measurement of sinus nodal recovery time before and after atropine. This appears to be especially useful in patients whose sinus nodal recovery time cannot be readily estimated because of junctional escape beats arising first during postpacing depression. In such cases, we consider the absence of response to atropine a valuable indication for permanent pacemaker insertion if the patient is symptomatic, even when Holter recording analysis is not contributory. In contrast, in the presence of a normal Holter recording, normal sinus nodal recovery time according to Scheinman's equation and a normal response to atropine in a patient with symptoms compatible with sinus nodal dysfunction, we recommend exploration of other possible causes of dizzy spells.

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References

1. **Reiffel JA, Bigger JT, Cramer M, et al:** Ability of Holter electrocardiographic recording and atrial stimulation to detect sinus nodal dysfunction in symptomatic and asymptomatic patients with sinus bradycardia. Am J Cardiol 40:189–194, 1977
2. **Scheinman MM, Kunkel FW, Peters RW:** Atrial pacing in patients with sinus node dysfunction. Am J Med 61:641–649, 1976

REPLY

In the conclusion of our paper, we suggested that additional maneuvers, such as tests of response to atropine, may improve ability to distinguish abnormal sinus nodal function from normal nodal behavior. Schoenfeld extends our discussion proposing atropine tests and use of the regression equation of Scheinman et al. for interpreting sinus nodal recovery time. We are encouraged by the preliminary results of these approaches but offer a note of caution about the interpretation of the latter two techniques.

Atropine: We find, as did Mandel et al.,[1] that a few patients with clearly established sick sinus syndrome have a subnormal increase in sinus rate after atropine. Until we criticized the practice, a single dose of 1 mg was the most prevalent atropine test for sinus nodal dysfunction. More recently, several investigators have used larger single doses, such as 0.04 mg/kg, hoping to achieve maximal cholinergic blockade. The 1 mg test can produce from 20 to 100 percent cholinergic blockade; the 0.04 mg/kg dose will nearly always produce maximal blockade but does not identify shifts in the heart rate response on the X axis of the dose-response curve. For the past 2 years, we have used full atropine dose-response curves for sinus nodal testing. This method permits us to determine: (1) the median effective dose for atropine, and (2) the heart rate (and its change) at maximal cholinergic blockade. This test removes the uncertainties associated with other methods of testing. Abnormal atropine dose-response curves do identify sinus nodal dysfunction. The converse is not true; a normal test can indicate that sinus dysfunction receives an important contribution from autonomic factors. One other caution should be sounded for atropine testing of sinus nodal function: Termination of atrial pacing or spontaneous cessation of spontaneous atrial tachyarrhythmias can be followed by a very long sinus nodal recovery time after atropinization.[2]

Regression equations for sinus nodal recovery time: As with atropine, there are difficulties in applying Scheinman's regression equation for sinus nodal recovery time. This regression equation was derived by pacing at two rates, 100 and 130 beats/min, in patients who had a normal heart rate. To apply the equation to patients with sinus bradycardia requires extrapolation of the regression line beyond the data points. The risk of such extrapolations in regression analysis is axiomatic. It is quite uncertain whether sinus bradycardia associated with sick sinus syndrome is significantly different from sinus bradycardia associated with excess vagal tone, hypothyroidism, antihypertensive drugs or other factors. Another problem is that patients with sick sinus syndrome reach their maximal sinus nodal recovery time at pacing rates lower than those used to generate the data for Scheinman's regression equation.[3,4] It is yet to be demonstrated that the regression approach as currently practiced will be sensitive and specific for predicting normal responses in patients with a slow heart rate. On the basis of the considerations briefly discussed here, we rather doubt it.

Our preceding remarks should not be construed as discouraging further attempts to refine the ability to recognize sinus nodal function in man. Quite the contrary. However, we do urge considerable circumspection in evaluating new tests proposed for this purpose.

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References

1. **Mandel WJ, Hayakawa H, Allen HN, et al:** Assessment of sinus node function in patients with the sick sinus syndrome. Circulation 46:761–769, 1972
2. **Reiffel JA, Bigger JT Jr, Giardina EGV:** "Paradoxical" prolongation of sinus nodal recovery time after atropine in the sick sinus syndrome. Am J Cardiol 36:98–104, 1975
3. **Reiffel JA, Bigger JT Jr, Cramer M, et al:** Paced cycle lengths of maximal corrected recovery times. Circulation 56:Suppl III:III-198, 1977
4. **Mandel W, Hayakawa H, Danzig R, et al:** Evaluation of sino-atrial node function in man by overdrive suppression. Circulation 44:59–66, 1971

VERAPAMIL AND SUDDEN DEATH

Corday et al.[1] suggest that verapamil, which specifically inhibits calcium uptake by the cell membrane, may prevent reentrant arrhythmias by blocking development of the calcium-dependent slow response action potential. They also quote Kaumann and Aramendia,[2] who found that 90 percent of dogs pretreated with verapamil were protected from ventricular fibrillation after acute coronary occlusion. Apparently they consider the administration of verapamil a promising approach to the problem of prevention of sudden death.

In fact, experimental data and human pathologic studies have shown that the drug is highly effective in the control of ventricular arrhythmias of ischemic myocardium. We[3] have administered verapamil intravenously to 12 patients with uncomplicated acute myocardial infarction who had persistent frequent ventricular premature complexes in the first 48 hours of illness. In all but one patient the drug quickly and definitively abolished the arrhythmia. This experience is too small to permit general conclusions, particularly in relation to prevention of sudden death, but it undoubtedly indicates that verapamil is effective in acute myocardial ischemia, a situation

in which ventricular arrhythmias are related to partly depolarized cells.[4]

Probably there are other clinical situations in which ventricular premature complexes are responsive to verapamil because they are related to slow responses of fast cells. Nevertheless, because it seems improbable that a fast cardiac fiber maintains a steady abnormal condition of slow response, these ought to be all situations in which acute cell damage is present. In the future might the responsiveness of ventricular extrasystoles to verapamil have some diagnostic implications for individuating these situations?

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References

1. **Corday E, Heng MK, Meerbaum S, et al:** Derangements of myocardial metabolism preceding onset of ventricular fibrillation after coronary occlusion. Am J Cardiol 39: 880–889, 1977
2. **Kaumann AJ, Aramendia P:** Prevention of ventricular fibrillation induced by coronary ligation. J Pharmacol Exp Ther 164:326–332, 1968
3. **Fazzini PF, Marchi F, Pucci P:** Effetto antiaritmico del verapamil sulla extrasistolia ventricolare dell'infarto miocardico acuto. G Ital Cardiol, in press
4. **Bigger JT, Dresdale RJ, Heissenbuttel RH, et al:** Ventricular arrhythmias in ischemic heart disease: mechanism, prevalence, significance and management. Prog Cardiovasc Dis 19:255–300, 1977

LOWN'S UNUSUAL CASE OF EFFORT ANGINA

Lown[1] has summarized the clinical evidence in effort angina that is inconsistent with the direct arteriosclerotic cause of this disorder and has illuminated these data with a compassionately recounted case report of a man with unusual effort angina. After initial effort caused chest pain, the patient sometimes felt a "switching of gears" and then could literally climb mountains. Conversely, by miscounting crossings during a Master's two-step test, it was possible to induce chest pain before the patient's usual tolerance limits were reached. To this observer, these apparently contradictory events are evidence for a dynamic and complex mechanism and are in favor of vasospasm.

Before we consider spasm as an explanation for the confusing features of effort angina, it seems mandatory to explain how spasm might cause the typical attributes of this disorder. How can stenotic coronary disease result in spasm, and how can spasm explain a quantitative relation between effort and angina?

Our explanation for angina,[2] including angina induced by effort, is based on the view that chronic myocardial damage from stenotic coronary artery disease favors the development of reflex injury-spasm. In effort angina, exertion causes the additional insult of acute myocardial ischemic injury, which then triggers the inappropriate injury reaction. (It is enigmatic how attacks of spasm are triggered in angina developing at rest.) In effort angina, the relation between the amount of exertion and the onset of chest pain is explained by the level of acute ischemic injury necessary to incite spasm. Also, for the same degree of coronary obstruction, the threshold for spasm varies from person to person, and many persons with severe coronary disease never experience angina.

The pathophysiology of coronary arterial spasm might be understood from the standpoint of the autoregulation of coronary blood flow. With myocardial ischemia, vasodilative metabolites are produced, and this is the basis of the anoxic-feedback mechanism for correcting ischemia. Therefore exertion in the presence of severe coronary artery disease should result in vasodilation. However, there also is a tendency toward the development of acute ischemic injury, which is vasoconstrictive. The occurrence of angina thus represents a dominance of vasoconstrictive over vasodilative forces. Also, once spasm develops, dynamics are altered. As spasm itself causes more ischemia, new and possibly differing levels of vasodilative and vasoconstrictive forces occur. Two directions seem possible. If injury-vasospasm continues to overbalance vasodilation, spasm is perpetuated and infarction ensues. If vasodilation supervenes, the attack of spasm is terminated. The anoxic-feedback mechanism is dose-dependent, and higher levels of ischemia probably are effective in reversing spasm. It is likely that the spontaneous relief of angina is related to the development of sufficient vasoactive metabolites to correct spasm.

In Lown's unusual case of effort angina,[1] after initial exertion caused chest pain, the ability to "switch gears" and then engage in strenuous exercise seems related to a beneficial dominance of vasodilative over vasoconstrictive forces at higher levels of ischemia. As Lown suggests, it is likely that the premature onset of angina with the miscounted Master's two-step test was due to an alteration of the autonomic nervous system by psychologic conditioning. This was expressed by a tendency for vasoconstriction which tipped the balance so that spasm occurred at a lower level of myocardial ischemia. Consistent with this view, a preponderance of parasympathetic activity has been suggested in infarction[2] and in variant angina.[3]

Coronary arterial autoregulation might provide the focus for an integrative pathogenetic mechanism for both the arteriosclerotic and psychologic factors in ischemic heart disease. The autonomic nervous system can be considered a secondary type of coronary arterial autoregulation,[2] operating through the coronary plexuses that innervate coronary arteries, and functioning in conjunction with the anoxic-feedback mechanism. A dual and cooperating system of coronary autoregulation provides a unifying link for the expression of both pathologic and psychic factors by the final common pathway of coronary arterial spasm.

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References

1. **Lown B:** Verbal conditioning of angina pectoris during exercise testing. Am J Cardiol 40:630–634, 1977
2. **Hellstrom HR:** The injury-vasospasm hypothesis of ischemic heart disease revisited. Am Heart J 94:624–648, 1977
3. **Yasue H, Touyama M, Shimamoto M, et al:** Role of autonomic nervous system in the pathogenesis of Prinzmetal's variant form of angina. Circulation 50:534–539, 1974

REPLY

The injury-vasospasm hypothesis that Helstrom propounds and has reviewed in some detail in a recent communication (his Ref. 2) is an attractive formulation that deserves serious consideration. Coronary arterial vasospasm, as an explanation for angina pectoris, is more consistent with clinical observations than the concept of myocardial hypoxia resulting from a mismatch between myocardial supply and demand. This latter viewpoint has gained sanction by frequent repetition and has been staunchly held since it was first promulgated by Keefer and Resnick[1] some 50 years ago.

Certainly in the patient I reported on the vagaries in occurrence of anginal episodes do not easily reconcile with the

belief that the chest discomfort originated in altered hemodynamic loads buffeting a myocardium underperfused because of extensive and fixed coronary arterial stenosis.

However, the theory of vasospasm, even when one brings on the stage the *deus ex machina* of autoregulatory feedback modulated by as yet undefined substances, leaves much unexplained. Why do some patients with extensive coronary artery disease never experience angina, while others with lesser involvement are severely disabled? The balancing between vasoconstrictor and vasodilator metabolites may indeed be true. But there is a need to identify these substances precisely as well as to define their specific triggers.

Current investigative work promises early clarification of the many factors that may be responsible for angina pectoris. But we need not limit ourselves to one outlook. For example, it is conceivable that transient platelet aggregates may induce vascular narrowing. In this context, the recent report by Folts and co-workers[2] is highly relevant. They demonstrated a cyclic reduction in coronary arterial flow to near zero in a vessel with fixed narrowing. The alterations in flow were due to platelet aggregations and disaggregations. Earlier, Jorgensen and associates[3] found that intracoronary injection of adenosine diphosphate in swine caused profound myocardial ischemic lesions that were preventable by prior induction of thrombocytopenia. It is now evident that platelets may release powerful vasoconstrictors like thromboxane A_2, while vascular endothelium liberates another prostaglandin, prostacyclin, that disaggregates platelets and relaxes arterial smooth muscle.

These important findings, I believe, still require the interplay of neural and neurohumoral factors if we are to account for the diverse clinical aspects of angina pectoris. In this context, it is significant that psychologic or physical stresses that release catecholamines into the circulation induce platelet aggregation in coronary arteries with ensuing myocardial lesions.[4] The syndrome so eloquently described by Heberden 2 centuries ago at last may yield the secret of its mechanisms.

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References

1. **Keefer CS, Resnik WH:** Angina pectoris: a syndrome caused by anoxemia of the myocardium. Arch Intern Med 41:769–807, 1928
2. **Folts JD, Crowell EB, Rowe CG:** Platelet aggregation in partially obstructed vessels and its elimination with aspirin. Circulation 54:365, 1976
3. **Jorgensen L, Rowell HC, Hovig T, et al:** Adenosine diphosphate-induced platelet aggregation and myocardial infarction in swine. Lab Invest 17:616, 1967
4. **Haft JI, Fani K:** Stress and induction of intravascular platelet aggregation in the heart. Circulation 48:164, 1973

SEPTAL PERFORATOR COMPRESSION IN IDIOPATHIC HYPERTROPHIC SUBAORTIC STENOSIS

We have analyzed 500 consecutive coronary arteriograms for the presence of septal perforator compression,[1] and our results are somewhat different from those of Pichard et al.[2] Like the latter, we found septal perforator compression in all 17 patients with idiopathic cardiomyopathy with idiopathic hypertrophic subaortic stenosis included in our series. However, we also observed this phenomenon in 4 of 10 patients with hypertrophic cardiomyopathy without obstruction, 11 of 18 patients with severe aortic stenosis (peak systolic gradient more than 70 mm Hg) (Fig. 1) and 3 of 17 patients with

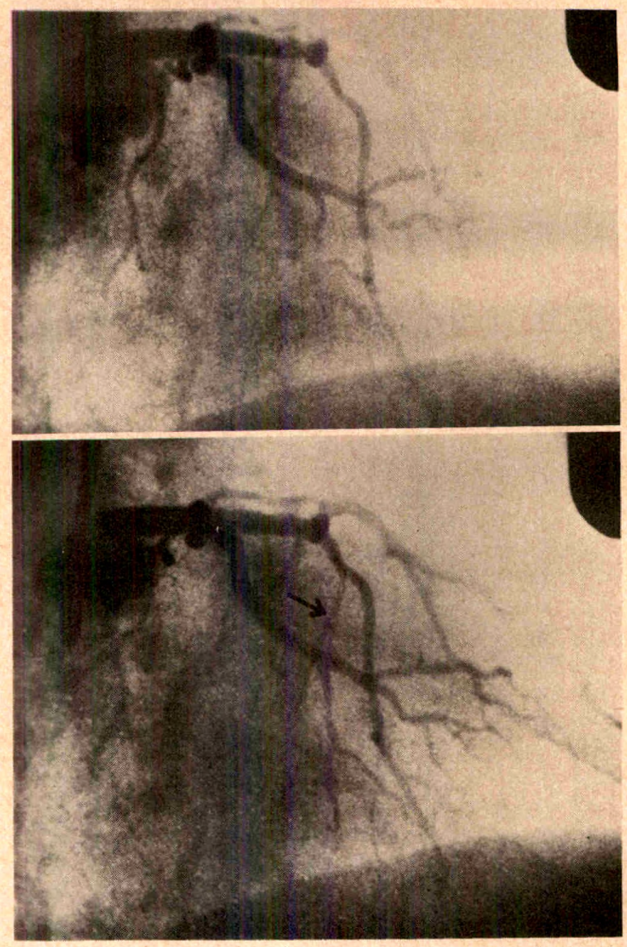

FIGURE 1. Septal perforator compression in a patient with severe aortic valve stenosis. **Upper frame,** systole. **Lower frame,** diastole. Note that the septal perforators that are visible during diastole **(lower frame, arrow)** disappear during systole.

mild or moderate aortic stenosis (peak systolic gradient less than 70 mm Hg). In addition, septal perforation compression was present in 4 of 17 patients with myocardial bridge and in 4 of 40 patients with subtotal occlusion (more than 95 percent stenosis) of the proximal left anterior descending coronary artery. It was not present in any of the 58 patients with a normal heart and normal coronary arteries, 4 patients with marked pulmonary hypertension (pulmonary arterial pressure at systemic levels) or 419 patients with other heart disease, including coronary artery disease, rheumatic heart disease, congenital heart disease, myocardial disease and cardiac tumors.

Septal perforator compression is thus seen not only in patients with idiopathic hypertrophic subaortic stenosis and cardiomyopathy, as suggested by the data of Pichard et al.,[2,3] but in those with a variety of cardiac conditions including aortic stenosis, myocardial bridge and critical stenosis of the left anterior descending coronary artery. These observations and the absence of septal perforation compression in patients with right ventricular pressure at systemic levels, in whom intramyocardial pressure would be similar across the septum, argue against the theory that the abnormal septal anatomy of idiopathic hypertrophic subaortic stenosis is the sole cause of this phenomenon. It appears that a decrease of the intraluminal septal perforator pressure due to an obstruction at the subaortic, aortic valve or coronary arterial level pre-

disposes to this phenomenon, which may be further facilitated by the abnormal septal anatomy of idiopathic hypertrophic subaortic stenosis or other conditions affecting the intraventricular septum.

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References

1. **Kostis JB, Moreyra AE, Natarajan N, et al:** "Septal squeeze." A coronary arteriographic clue to the diagnosis of IHSS (abstr). Proc International Congress of Cardiovascular Surgery, Athens, Greece, June 1977, p 115
2. **Pichard AD, Meller J, Teichholz LE, et al:** Septal perforator compression (narrowing) in idiopathic hypertropic subaortic stenosis. Am J Cardiol 40:310–314, 1977
3. **Pichard A, Meller J, Teichholz L, et al:** Septal perforator compression in idiopathic hypertrophic subaortic stenosis: a patho-physiologic maker (abstr). Circulation 54: Suppl II:II–105, 1976

REPLY

After receiving the letter from Kostis and Moreyra, I went to their cardiac laboratory and personally reviewed examples of their cases of aortic stenosis and coronary disease with septal perforator compression. Their patients did manifest septal perforator compression although it was by no means as prominent as the phenomenon seen in idiopathic hypertrophic subaortic stenosis. All of their patients with aortic stenosis and septal compression had marked left ventricular hypertrophy in addition to hypercontractility with a contraction pattern identical to that seen in idiopathic hypertrophic subaortic stenosis.

This has not been our experience. In the last 40 consecutive cases of aortic stenosis, we have not seen septal perforator compression. We do have one patient in our earlier series with aortic stenosis and minimal septal perforator compression. This discordance appears most interesting. We hope that future research will explain the underlying mechanism of the visual phenomenon of septal perforator compression.

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CLINICAL CORRELATES OF LEFT VENTRICULAR CAVITY OBLITERATION

The article by Raizner et al.[1] would have benefited by the addition of a master table describing each individual patient. It is now impossible to trace any individual patient, and some points are not clear. For example, what were the characteristics of the patients who presented systolic anterior motion, and did these patients happen to be the ones who also had mitral regurgitation? Which patients showed mitral valve prolapse—the ones with asymmetric septal hypertrophy or the ones without it? Also, the text states that nine patients had the Brockenbrough phenomenon, but I could trace only seven. Probably the missing two belonged to the group of patients that did not have satisfactory echocardiograms, but I would have liked to know their hemodynamic status. In addition, it would have been interesting to know the response of the left ventricular end-diastolic pressure to angiographic stress and what the carotid or aortic tracings looked like. Did patients with cavity obliteration and *no asymmetric septal hypertrophy* also have bisferiens pulses?

Finally, their discussion of the mechanism of the postextrasystolic beat phenomenon in cavity-obliterating ventricles (impaired ventricular filling leading to *less* postextrasystolic diastolic stretch and maximal or near maximal ejection fraction during sinus rhythm *minimizing* any inotropic enhancement that may follow the premature complex), leads me to the opposite conclusion, that is, that the postextrasystolic beat phenomenon should *not* occur. Still, it does occur; thus, there is something wrong in the logic of the explanation; perhaps, there *is* good diastolic filling after a premature complex, after all. Reviewing the echocardiograms might show some premature ventricular complexes occurring while the left ventricular cavity was being visualized. The recently described noninvasive technique for evaluating postextrasystolic potentiation with echocardiography should be of help on this point.

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References

1. **Raizner AE, Chahine RA, Ishimori T, et al:** Clinical correlates of left ventricular cavity obliteration. Am J Cardiol 40:303–309, 1977
2. **Cohn PF, Angoff GH, Zoll PM, et al:** A new, noninvasive technique for inducing postextrasystolic potentiation during echocardiography. Circulation 56:598–604, 1977

REPLY

The manuscript as originally submitted did contain a master table; however, this was changed to a summary table at the suggestion of reviewers who believed, appropriately, that the master table was somewhat tedious. Nevertheless, I think we can clarify some specific points of information.

1. Of the three patients with systolic anterior motion of the anterior leaflet of the mitral valve, two had resting intraventricular pressure gradients (one of whom also had a transvalve aortic stenosis gradient) and all three had symmetric septal hypertrophy (septum to posterior wall ratio less than 1.3). Mitral regurgitation was not observed in these three patients.

2. Among the patients with angiographic mitral valve prolapse, echocardiographic data in four revealed symmetric (three) and asymmetric (one) septal hypertrophy. In patients with cavity obliteration, the mitral valve apparatus, although normal, may be disproportionately large for the obliterated cavity, resulting in mitral prolapse.

3. The Brockenbrough, or postextrasystolic beat, phenomenon was seen in nine patients. As Val-Mejias points out, echocardiographic data were not available in two patients. These two patients had no intraventricular pressure gradient, and their findings further reinforce the suggestion that cavity obliteration in itself, without obstructive phenomena, might have important hemodynamic significance.

4. Left ventricular end-diastolic pressure after angiography ranged from 7 to 30 mmHg (mean 18.6 ± 1.5 mm Hg). Thirteen of the 24 patients manifested an abnormally elevated (greater than 18 mm Hg) postangiographic left ventricular end-diastolic pressure.

5. We did not systematically record external carotid pulse tracings; hence we do not have data ralative to the incidence of this finding.

Clearly, many fascinating clinical correlations may be made in a study of this sort. It would be impossible to discuss all such correlations in a readable paper. We hope we have provided some of the specific information requested.

The final point reflects a question of nomenclature. The postextrasystolic beat phenomenon is synonymous with the Brockenbrough phenomenon and is defined as a decrease in the arterial pulse pressure in the sinus beat following an extrasystole.[1] Thus, it is an abnormal finding that has been said to be relatively specific for idiopathic hypertorphic subaortic stenosis, but which we have found in patients with cavity obliteration who do not have other evidence of idiopathic hypertrophic subaortic stenosis.

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Reference

1. **Brockenbrough EC, Braunwald E, Morrow AG:** A hemodynamic technic for the detection of hypertrophic subaortic stenosis. Circulation 23:189–194, 1961

LEUKOCYTIC SCINTIGRAPHY AFTER CARDIAC TRANSPLANTATION

Weiss et al.[1] recently reported a technique for imaging of the inflammatory response in ischemic myocardium with ^{111}Indium-labeled leukocytes. They suggest that, in addition to detection of myocardial infarction, this technique may prove useful in detecting bacterial endocarditis, myocarditis and pericarditis. Another potentially useful application they did not mention might be detection of acute rejection in patients with a cardiac transplant. Current noninvasive techniques for diagnosing this process are relatively nonspecific. Endomyocardial biopsy, the current procedure of choice for definitive diagnosis, is an invasive procedure with some risk. Therefore, leukocytic scintigraphy might be a useful addition to the diagnostic tools for managing patients after cardiac transplantation.

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Reference

1. **Weiss ES, Ahmed SA, Thako ML, et al:** Imaging of the inflammatory response in ischemic canine myocardium with ^{111}Indium-labeled leukocytes. Am J Cardiol 40:195–199, 1977

REPLY

We concur that scintigraphy with labeled leukocytes, and for that matter other cell types, may be useful in evaluating possible rejection among patients with a cardiac transplant. As we indicated in our paper, the technique was developed not only to evaluate ischemic myocardium, but also to provide a new tool for assessing cell responses within the heart to a variety of pathophysiologic conditions. The one Gillum suggests is indeed attractive and appears to merit objective evaluation in experimental animals and possibly in man.

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CALENDAR OF EXTRAMURAL PROGRAMS

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Extramural Programs Department, Division of Continuing Education, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

SEPTEMBER 1978 THROUGH OCTOBER 1978

To be arranged individually Preceptorships in Cardiology. Arthur Selzer, FACC, director, Pacific Medical Center, San Francisco, CA

SEPT. 7–9 **The Clinical Pharmacology of Cardiovascular Drugs.** William B. Abrams, FACC, Albert N. Brest, FACC, Richard O. Davies, FACC and Roger F. Ferguson, co-directors. Marriott Motor Hotel, Philadelphia, PA

SEPT. 11–14 **Electrocardiography: Core Curriculum and Self-Assessment.** Paul L. McHenry, FACC, director and Charles Fisch, FACC, co-director. Myers Auditorium, Wishard Memorial Hospital, Indiana University Medical Center, Indianapolis, IN

SEPT. 11–14 **Electrocardiography: Core Curriculum and Self-Assessment.** Arthur Selzer, FACC, director. Golden Gateway Holiday Inn, San Francisco, CA

SEPT. 27–29 **Advanced Echocardiography.** Harvey Feigenbaum, FACC, director and Betty C. Corya, James C. Dillon, FACC and Arthur E. Weyman, FACC, co-directors. Indianapolis Hilton Hotel, Indianapolis, IN

OCT. 12–14 **Cardiology Update—1978.** William W. Parmley, FACC and Kanu Chatterjee, FACC, directors. Del Monte Hyatt House, Monterey, CA

OCT. 13–14 **Geriatric Cardiology. Physiologic vs. Pathologic Aging of the Cardiovascular System: Clinical Applications and Therapeutic Considerations.** Borys Surawicz, FACC and Raymond Harris, FACC, directors. Hyatt Regency Lexington, Lexington, KY

OCT. 18–20 **Cardiac Pacing.** Doris J. W. Escher, FACC and Seymour Furman, FACC, directors. Waldorf-Astoria Hotel, New York, NY

OCT. 19–21 **Valvular Disease—Practical Diagnosis and Management.** Peter C. Gazes, FACC, director and Charles P. Summerall III, FACC, Grady H. Hendrix, FACC, William H. Barnwell II, FACC, Bruce W. Usher, FACC, J. Lindsay Leviner, Jr. and Robert G. Irvin, co-directors. Kiawah Island Inn, Kiawah Island, Charleston, SC

LEARNING CENTER: PROGRAM CALENDAR

The American College of Cardiology's newest department, the Learning Center, located at the College's Bethesda, Maryland headquarters, began operations last October with the offering of its first continuing medical education program for physicians with a specialty or an interest in cardiovascular medicine. The purpose of the Learning Center is to support the professional commitment to quality patient care by providing a new standard of excellence in cardiovascular continuing education. For additional information concerning the programs listed below or for a complete schedule of programs through December 1978, contact Program Coordinator, Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014. Telephone (301) 897-5400.

SEPTEMBER THROUGH DECEMBER 1978

Month/Dates	Course Director	Title of Program
September 25–27	Kenneth M. Rosen, MD, FACC	**Evaluation of Arrhythmias with His Bundle Recording and Cardiac Stimulation**
October 4–6	Charles E. Rackley, MD, FACC	**Clinical Evaluation and Treatment of Coronary Artery Disease**
October 19–21	Pravin M. Shah, MD, FACC	**Adult Echocardiography: Clinical Applications–M-Mode vs 2-Dimensional**
October 23–25	Douglas P. Zipes, MD, FACC	**The Ubiquitous PVC: Sorting Out the Dilemma**
November 6–9	Ralph Shabetai, MD, FACC	**Management of Pericardial and Myocardial Disease**
December 4–6	Borys Surawicz, MD, FACC	**Advanced Cardiac Electrophysiology and Electrocardiography**
December 11–13	Victor Parsonnet, MD, FACC	**Current Concepts in Pacing: An Individualized Seminar Approach**

28th ANNUAL SCIENTIFIC SESSION AMERICAN COLLEGE OF CARDIOLOGY

Miami Beach, Florida **March 11–15, 1979**

- **Abstracts**
  Entries must be postmarked no later than September 18, 1978
- **Technical Exhibits**
  Deadline for requests for space: October 2, 1978
- **Scientific Exhibits**
  Deadline for requests for space: October 2, 1978
- **Young Investigators' Awards Competition**
  Entries must be postmarked no later than November 1, 1978

For application forms, write Patrick A. Ziarnik, Director, Annual Scientific Session Department, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

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Those desiring an application form should write to Ms. Margaret E. Coffey, Director, Membership Department, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

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THE WHOLE PAPER

- Address manuscript to Managing Editor, American Journal of Cardiology, 666 Fifth Ave., New York, NY 10019.
- Submit two copies of all elements of the article: text, references, legends, tables and figures.
- Arrange the paper in this order: (1) title page; (2) abstract; (3) text; (4) references; (5) legends; (6) tables; and (7) figures.
- Number all pages in above sequence, beginning with title page as 1, abstract as 2, etc.
- Type all matter: (1) on 8½ × 11 opaque white bond paper; (2) in duplicate; (3) on one side of each sheet only; (4) double-space; (5) leave wide margins, all four sides.

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- Include first names, degrees and, where applicable, FACC for all authors.
- Provide a short running title of 3 to 6 words.
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28. Schiebler GL, Van Mierop LHS, Krovetz LJ: Diseases of the tricuspid valve, chap 20. In, Heart Disease in Infants, Children and Adolescents (Moss AJ, Adams F, ed). Baltimore, Williams & Wilkins, 1968, p 134

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36. Berne E: Principles of Group Treatment. New York, Oxford University Press, 1966, p 26

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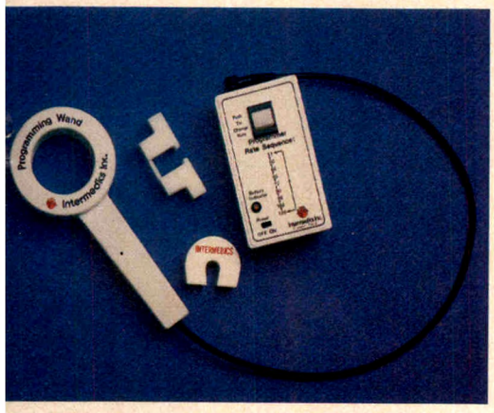

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Note: The InterLith-RP is currently being clinically evaluated.
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INTERMEDICS PULSE GENERATORS

INDICATIONS FOR USE Implantable cardiac pulse generators may be indicated for long-term treatment of impulse formation and conduction disorders resulting in symptomatic bradyarrhythmias, tachyarrhythmias, and heart block unresponsive to drug therapy.

PRECAUTIONS Implanted pacemakers have a finite and relatively widely variable service life as a result of factors such as the initial capacity of the battery and the shelf storage time of the manufactured pacemaker; variations in electrode system resistances, stimulation rate, and the percentage of time the implanted pacemaker is inhibited; and random electronic component failures.

Pacemaker operation can be influenced by electric, magnetic, or electromagnetic energy mimicking normal cardiac activity. In addition, certain environmental sources can couple sufficient energy into a pacemaker system to damage the pulse generator. Specifically, diathermy should not be used on pacemaker patients because of possible total inhibition of the pulse generator; electrocautery can inhibit and/or damage the pacemaker as well as cause burns or possible ventricular fibrillation; defibrillation can damage the pacemaker, and the presence of the pacemaker may cause increased cardiac muscle damage from defibrillation. Certain electrical and gasoline-powered appliances can cause inhibition of an implanted cardiac pacemaker system.

For complete precautions, see the Physician's Manual for the Intermedics cardiac pulse generator to be used.

CONTRAINDICATIONS AND SIDE EFFECTS There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. Body rejection phenomena, local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

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(spironolactone 25 mg./
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WARNING

Spironolactone, an ingredient of Aldactazide, has been shown to be a tumorigen in chronic toxicity studies in rats (see *Warnings*). Aldactazide should be used only in those conditions described under *Indications*. Unnecessary use of this drug should be avoided.

Fixed-dose combination drugs are not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Indications: Cirrhosis of the liver accompanied by edema and/or ascites. Essential hypertension, edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate.

Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, hyperkalemia or acute or severe hepatic failure. Allergy to thiazide diuretics or to other sulfonamide-derived drugs.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactazide. Do not administer concurrently with other potassium-sparing diuretics. Sulfonamide derivatives including thiazides have been reported to exacerbate or activate systemic lupus erythematosus.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75 and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hypokalemia may develop as a result of profound diuresis, particularly when Aldactazide is used concomitantly with loop diuretics, glucocorticoids or ACTH. Transient elevation of BUN may occur. Dilutional hyponatremia or rarely low-salt syndrome may develop. Gynecomastia may develop and in rare instances some breast enlargement may persist.

Thiazides may alter the metabolism of uric acid and carbohydrates with possible hyperuricemia, gout and decreased glucose tolerance. Vascular responsiveness to norepinephrine is reduced. Thiazides may also increase the responsiveness to tubocurarine. Thiazides may decrease serum PBI levels and prolonged therapy may induce hypercalcemia and hypophosphatemia.

Spironolactone may and hydrochlorothiazide does cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. Breast feeding should be discontinued when Aldactazide is being used.

Adverse Reactions:

Associated with spironolactone: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established.

Associated with thiazides: Gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhea, abdominal cramps), purpura, thrombocytopenia, leukopenia, agranulocytosis, dermatologic symptoms (cutaneous eruptions, pruritus, erythema multiforme), paresthesia, acute pancreatitis, jaundice, dizziness, vertigo, headache, xanthopsia, photosensitivity, necrotizing angiitis, aplastic anemia, orthostatic hypotension, muscle spasm, weakness and restlessness.

Adverse reactions are usually reversible upon discontinuation of Aldactazide.

Dosage and Administration

Edema in adults: The usual maintenance dose is one tablet four times daily but may range from one to eight tablets daily depending on the response to the initial titration.

Edema in children: The usual daily maintenance dose should be that which provides 0.75 to 1.5 mg. of spironolactone per pound of body weight (1.65 to 3.3 mg./kg.).

Essential hypertension: Usually two to four tablets daily depending on results of the titration of the individual ingredients.

SEARLE **Searle & Co.**
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Aldactazide...effective antihypertensive/diuretic therapy over the long run with less chance of refractoriness.
PLUS...a unique potassium safety valve.
Only ALDACTAZIDE has a unique mode of action that maintains potassium stores to help prevent hypokalemia with limited risk of hyperkalemia.
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Aldactazide®
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Effective antihypertensive/diuretic therapy PLUS a potassium safety valve—when you feel other measures won't do.
As with any potassium-sparing diuretic/antihypertensive, if renal impairment exists or if potassium supplements are administered during ALDACTAZIDE therapy, hyperkalemia may occur.
When other measures are inadequate or inappropriate to control hypertension, consider ALDACTAZIDE.
Fixed-dose combination drugs are not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management.
Before prescribing, please consult the complete prescribing information, a brief summary of which appears on the facing page.

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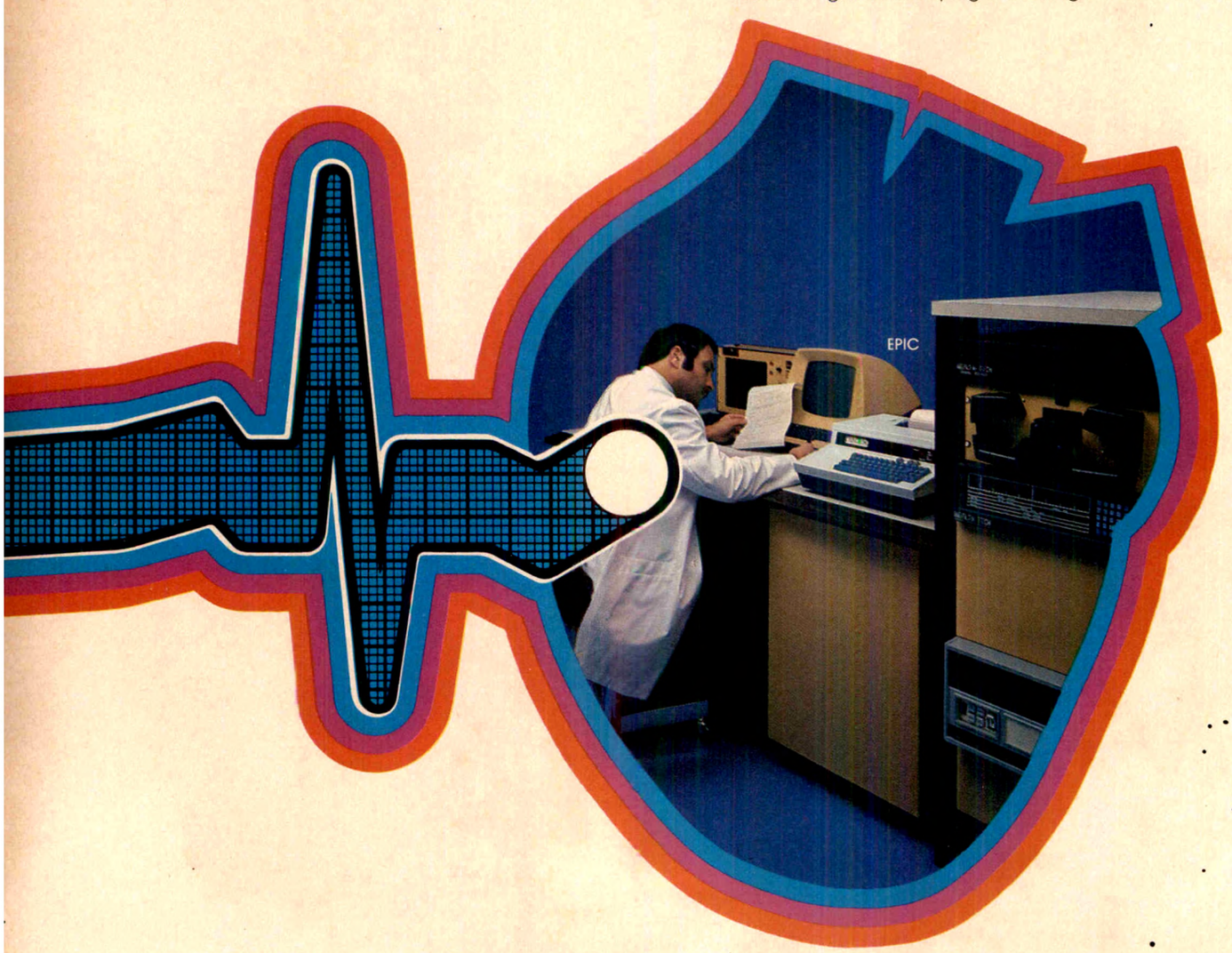

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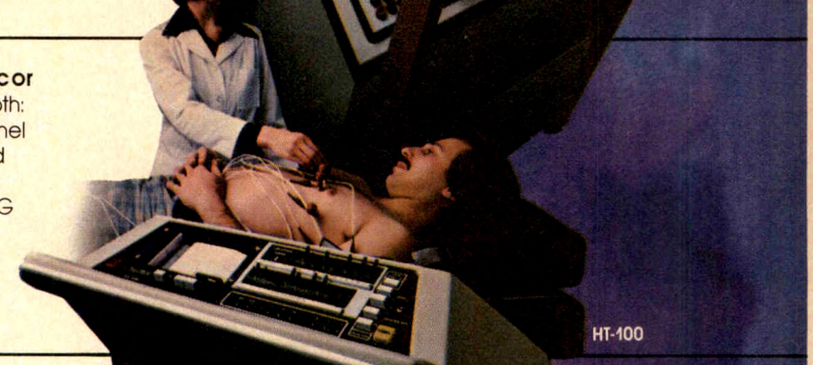

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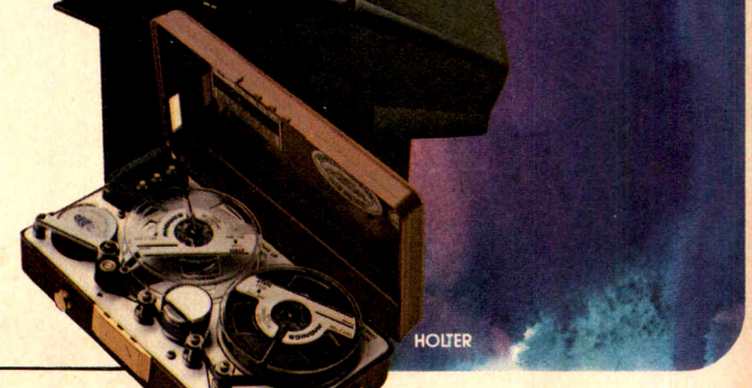

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New cardiac catheterization studies demonstrate prolonged changes for over 5 hours in cardiac hemodynamics with PERITRATE® 40-mg ORAL TABLET

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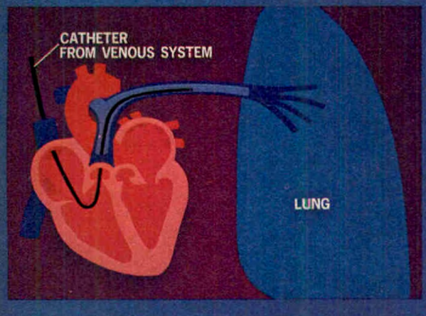
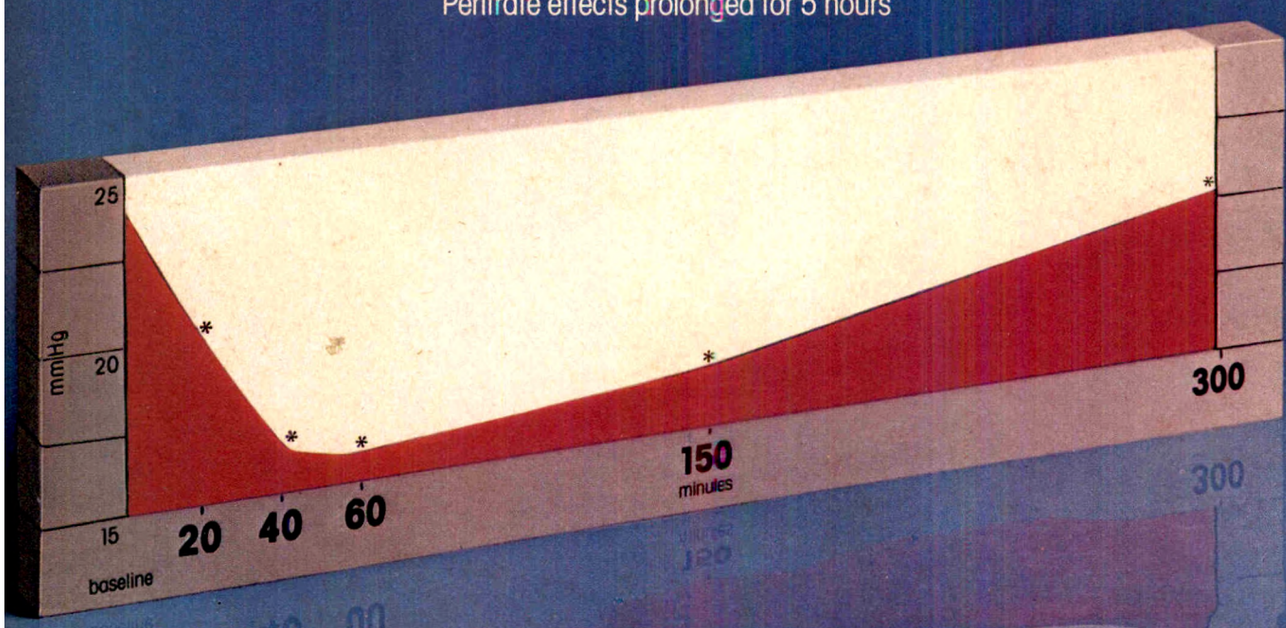


In a randomized double-blind study of catheterized patients with congestive heart failure, Peritrate 40 mg demonstrated marked changes in a variety of hemodynamic parameters with no change in heart rate.[1]

A marked reduction in PRELOAD: Peritrate reduced pulmonary arterial wedge pressure for over 300 minutes. The maximum reduction was 37%. Pulmonary arterial mean pressure was also reduced for over 300 minutes. These manifestations of reduced PRELOAD resulted from an increase in venous capacitance leading to a reduction in left ventricular end-diastolic volume and pressure. The observed reduction in pulmonary wedge pressure indicates marked preload reduction.

Peritrate effects prolonged for 5 hours



A reduction in AFTERLOAD: A significant reduction of arterial blood pressure, correlating with reduced AFTERLOAD, was maintained for over 300 minutes.[1]

Reduction in blood pressure for 5 hours

parameter	before Peritrate n=12	60 minutes after Peritrate n=12	150 minutes after Peritrate n=12	300 minutes after Peritrate n=8
blood pressure (mmHg) systolic	122.6	116.7*	116.9	116.8*
diastolic	68.7	63.4*	61.3*	61.0*

*Statistically significant at the 5% level.

Peritrate actions observed

- Activity was prolonged for at least 5 hours.
- PRELOAD and AFTERLOAD showed a marked reduction lasting at least 5 hours.

1. Klein RC, Amsterdam EA, Pratt C, et al: Sustained reduction of elevated left ventricular filling pressure in cardiac failure by oral, long-acting nitrate therapy. Presented at The American Federation for Clinical Research, San Francisco, Calif, April 29-May 1, 1978.

Please see following page for brief summary of prescribing information.

Conclusions

1. The prolonged reduction in preload and afterload reduces the amount of energy expended and oxygen consumed by the heart. This reduction in oxygen demand should relieve or prevent angina.
2. Provides a smooth onset of action without tachycardia. Unwanted effects are rare, and patient compliance is excellent.

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CAUTION: Federal law prohibits dispensing without prescription.
Description: Each tablet of Peritrate SA Sustained Action contains: pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Each tablet of Peritrate 40 mg contains pentaerythritol tetranitrate 40 mg. Each tablet of Peritrate 20 mg contains pentaerythritol tetranitrate 20 mg. Each tablet of Peritrate 10 mg contains pentaerythritol tetranitrate 10 mg. Peritrate (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg and Peritrate (pentaerythritol tetranitrate) are contraindicated in patients who have a history of sensitivity to the drug.
Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.
Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.
Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe, persistent headaches may occur.

In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:

(a) Cutaneous vasodilatation with flushing.
(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.
(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

Dosage: Peritrate (pentaerythritol tetranitrate) may be administered in individualized doses up to 160 mg a day. Dosage can be initiated at one 10 mg or 20 mg tablet q.i.d. and titrated upward to 40 mg (two 20 mg tablets or one 40 mg tablet) q.i.d. one-half hour before or one hour after meals and at bedtime. Alternatively, Peritrate Sustained Action 80 mg can be administered on a convenient b.i.d. dosage schedule.
Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg—double-layer, biconvex, dark green/light green tablets in bottles of 100 (N 0047-0004-51) and 1000 (N 0047-0004-60). Also unit dose, package of 10 x 10 strips (N 0047-0004-11).

Peritrate (pentaerythritol tetranitrate) 40 mg—pink scored tablets in bottles of 100 (N 0047-0008-51).

Peritrate (pentaerythritol tetranitrate) 20 mg—light green, scored tablets in bottles of 100 (N 0047-0001-51) and 1000 (N 0047-0001-60). Also unit dose, package of 10 × 10 strips (N 0047-0001-11).

Peritrate (pentaerythritol tetranitrate) 10 mg—light green, unscored tablets in bottles of 100 (N 0047-0007-51) and 1000 (N 0047-0007-60).
STORE BETWEEN 59° and 86° F (15° and 30° C).
Animal Pharmacology: In a series of carefully designed studies in pigs, Peritrate (pentaerythritol tetranitrate) was administered for 48 hours before an artifically induced occlusion of a major coronary artery and for seven days thereafter. The pigs were sacrificed at various intervals for periods up to six weeks. The result showed a significantly larger number of survivors in the drug-treated group. Damage to myocardial tissue in the drug-treated survivors was less extensive than in the untreated group. Studies in dogs subjected to oligemic shock through progressive bleeding have demonstrated that Peritrate (pentaerythritol tetranitrate) is vasoactive at the postarteriolar level, producing increased blood flow and better tissue perfusion. These animal experiments cannot be translated to the drug's actions in humans.
Full information is available on request.

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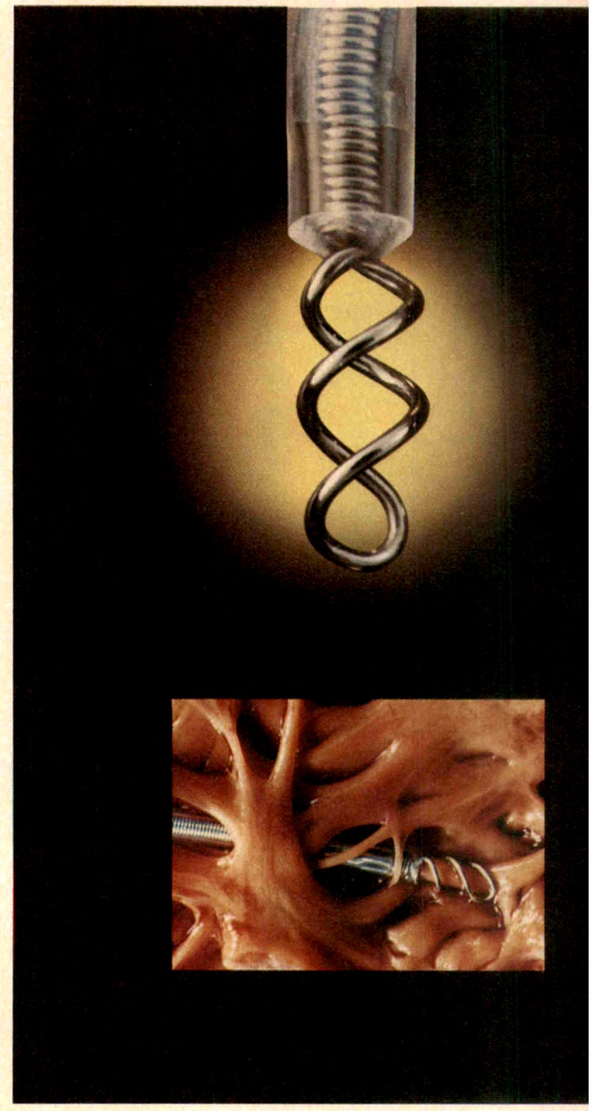

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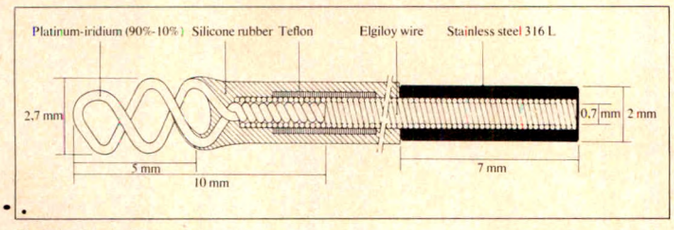

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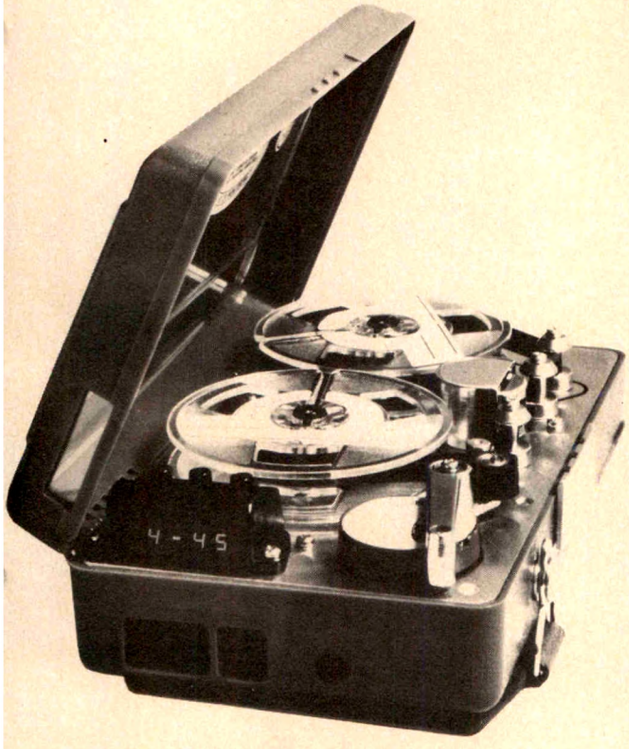

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THROMBOEMBOLISM

COUMADIN® (CRYSTALLINE SODIUM WARFARIN U.S.P.)

FOR ORAL ANTICOAGULATION

Prophylactic Use

A number of cardiac syndromes can predispose patients to thromboembolic episodes. The greatest threat of thromboembolism, however, exists in patients with a history of obesity, excessive cigarette smoking or previous episodes of venous thrombosis or pulmonary embolism. Postoperative patients requiring extended immobilization and the elderly are at high thromboembolic risk as are the severely injured—particularly those over 40 years with fractures of the hip, pelvis or lower extremities—and patients undergoing elective cup arthroplasty or pelvic surgery.

Emphasis should be placed on prophylaxis for those patients predisposed to thromboembolism. The oral anticoagulant of choice is COUMADIN® (crystalline sodium warfarin U.S.P.)

Therapeutic Use

For established thromboembolism, administration of I.V. heparin followed by oral anticoagulant therapy is a cornerstone of treatment. COUMADIN,® a chemically pure oral anticoagulant with high predictability of response, is a mainstay of effective therapy.

Dosage and Administration

In patients receiving COUMADIN,® prothrombin time should be maintained at 1.5 to 2.5 times the control until results stabilize. Dosage and administration should be individualized according to prothrombin time results and reevaluated periodically throughout therapy.

Patients should be well informed about their condition and medication, since factors such as dietary change, travel, other medication, change in physical condition and abrupt environmental change may influence prothrombin time and, therefore, response to COUMADIN.®

The oral anticoagulant of choice COUMADIN®

(CRYSTALLINE SODIUM WARFARIN U.S.P.)

Endo Laboratories, Inc.

Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

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Before prescribing, please see prescribing information on following page.

COUMADIN® is an Endo registered U.S. trademark;
U.S. Pat. No. 3,077,481 (Reissue No. 25,866)

COUMADIN®

(CRYSTALLINE SODIUM WARFARIN*)

DESCRIPTION COUMADIN® (crystalline sodium warfarin), a prothrombinopenic anticoagulant, is chemically crystalline sodium warfarin isopropanol clathrate. The crystallization of sodium warfarin virtually eliminates trace impurities present in amorphous sodium warfarin, thus achieving a crystalline product of the highest purity. Warfarin is the coined generic name for 3-(α-Acetonylbenzyl)-4-hydroxycoumarin. On a dose-for-dose basis, COUMADIN® (crystalline sodium warfarin) is therapeutically equivalent to amorphous sodium warfarin.

ACTIONS COUMADIN® and other coumarin anticoagulants act by depressing synthesis in the liver of several factors which are known to be active in the coagulation mechanisms in a variety of diseases characterized by thromboembolic phenomena. The resultant **in vivo** effect is a sequential depression of Factors VII, IX, X and II. The degree of depression is dependent upon the dosage administered. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombosis has occurred, anticoagulant treatment aims to prevent further extension of the formed clot and prevents secondary thromboembolic complications which may result in serious and possible fatal sequelae.

After oral administration, absorption is essentially complete, and maximal plasma concentrations are reached in 1 to 9 hours. Approximately 97% is bound to albumin within the plasma. COUMADIN® usually induces hypoprothrombinemia in 36 to 72 hours, and its duration of action may persist for 4 to 5 days, thus producing a smooth, long lasting response curve. Little is known of the metabolic pathways involved in the biotransformation of oral anticoagulants in man. However, their metabolites appear to be eliminated principally in the urine.

INDICATIONS Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN® is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Pregnancy—COUMADIN® (crystalline sodium warfarin) is contraindicated in pregnancy because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy. Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms–cerebral, dissecting aorta; (4) pericarditis and pericardial effusions; (5) subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis; or lack of patient cooperation. **Spinal puncture** and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding. **Miscellaneous:** polyarthritis, vitamin C deficiency, major regional, lumbar block anesthesia and malignant hypertension.

WARNINGS Sodium warfarin is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN® are given together, a period of 4 to 5 hours should elapse after the last intravenous dose and 12 to 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when sodium warfarin is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:
Lactation–coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Prolonged dietary deficiency** (cachexia, vitamin K). **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**–sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, menometrorrhagia, allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN®, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN®.

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders–infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency–steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cinchophen; clofibrate; COUMADIN® overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methyldopa; methylphenidate; metronidazole; monoamine oxidase inhibitors; nalidixic acid; oxolinic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates; sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; trimethoprim/sulfamethoxazole; unreliable prothrombin time determinations.

†Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN® underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN®. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN® (crystalline sodium warfarin) include:

1. Minor or major hemorrhage from any tissue or organ–which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and an extremely rare reaction consisting of hemorrhagic infarction and necrosis of the skin.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN® patient aids are available to physicians on request.

The administration and dosage of COUMADIN® must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K dependent Factors VII, X and II. These factors, in addition to Factor IX, are affected by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN® should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic prothrombinopenia are 1½ to 2½ times the normal prothrombin time (e.g. 21 to 35 seconds, with a control of 14 seconds).

Induction–40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Maintenance–Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy–The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery–The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN® be adjusted to maintain the prothrombin time at approximately 1½ to 2 times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN® with Heparin–Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in situations of great emergency to administer sodium heparin initially along with COUMADIN®. The initial dose of heparin and injectable COUMADIN® may be administered together in the same syringe. It should be noted that heparin may affect the prothrombin time, and therefore, when patients are receiving both heparin and COUMADIN®, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, and preferably 4 to 5 hours after the last intravenous injection or 12 to 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN® (crystalline sodium warfarin), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN® may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN® administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can be obtained.

SUPPLIED Tablets: COUMADIN® (crystalline sodium warfarin). For oral use, single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white, 25 mg red. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100.

Injection: Available as single injection units of amorphous sodium warfarin lyophilized for intravenous or intramuscular use in a box of 6 units for use immediately after reconstitution. 50 mg: Unit consists of 1 vial, 50 mg; sodium chloride, 10 mg; thimerosal, 0.2 mg. pH is adjusted with sodium hydroxide; accompanied by a 2 ml ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

*Present as crystalline sodium warfarin isopropanol clathrate.

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March, 1977

CARDIOLOGY: Update

Editor-in-Chief:
Henry A. Solomon, M.D., F.A.C.P., F.A.C.C.,
Clinical Assistant Professor of Medicine,
(Cardiology), Cornell University Medical College

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Clinical Recognition and Management
of Heart Disease – 1978
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April 3 - 7, 1978
New York, NY
Consultant's Course in Cardiology

April , 1978
Las Vegas, Nevada
Cardiac Imaging – 1978

May 12 - 14, 1978
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in Ischemic Heart Disease

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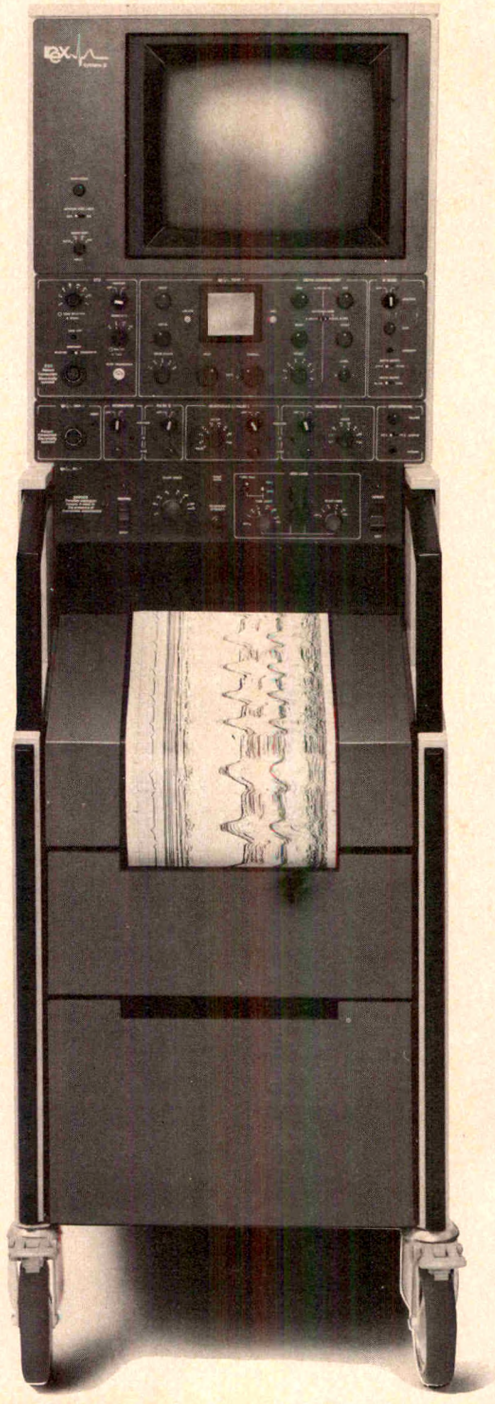

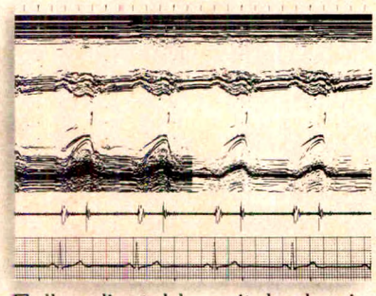

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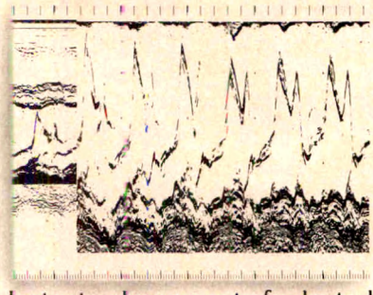

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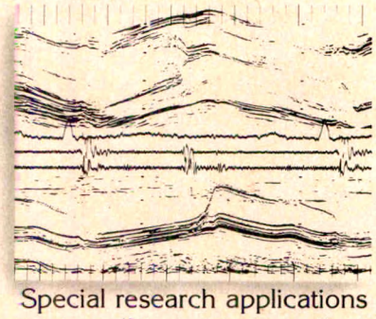

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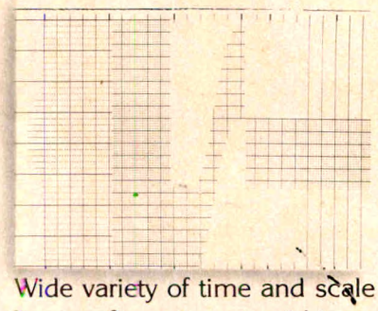

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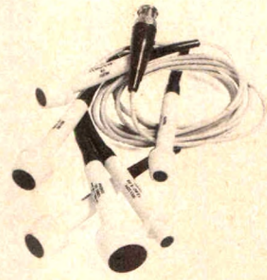

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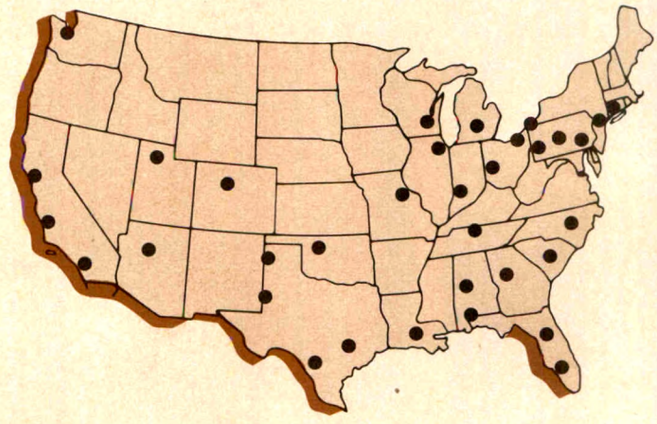

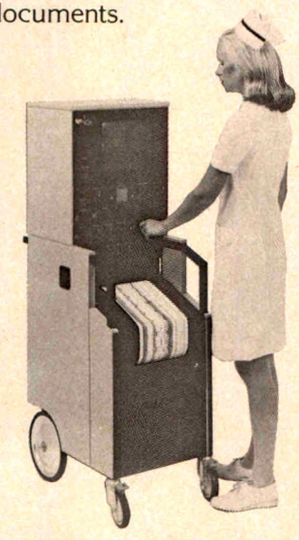

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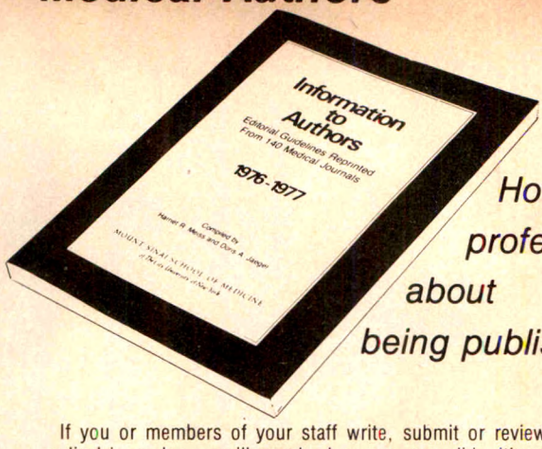

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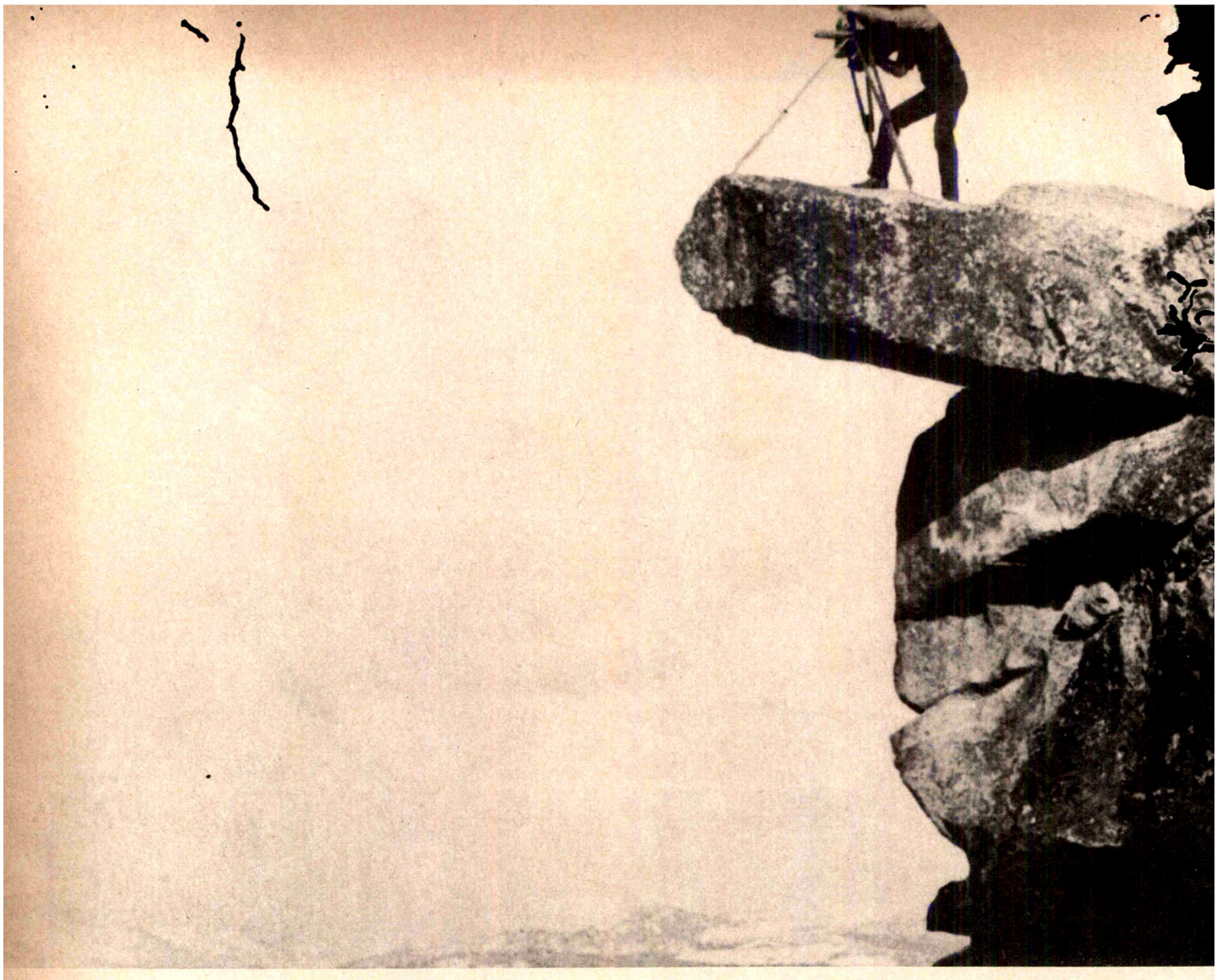

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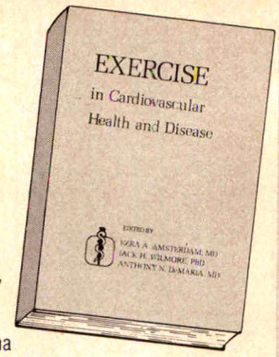

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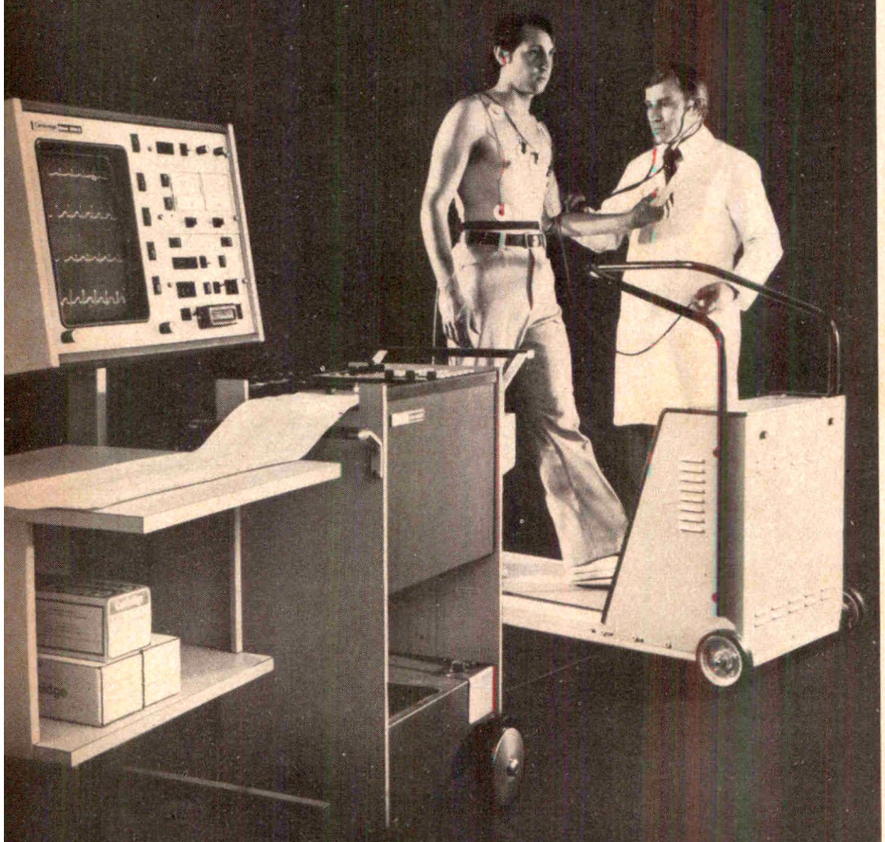

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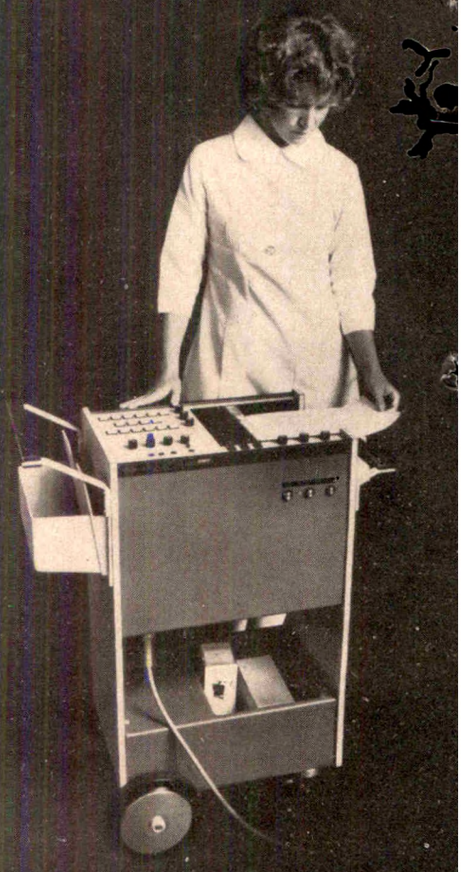

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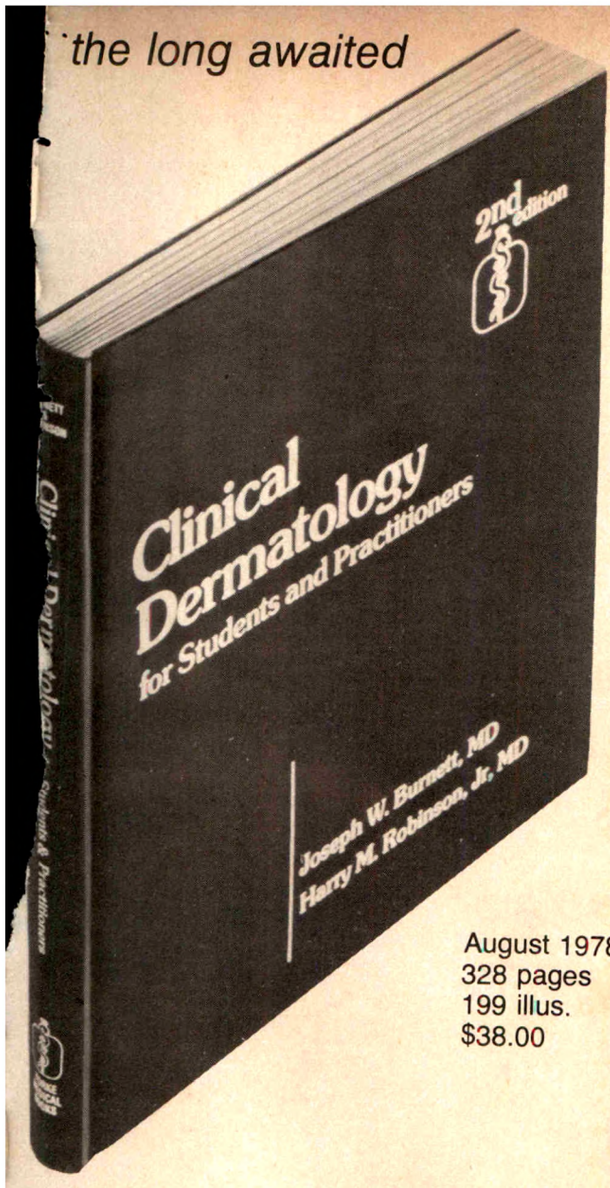

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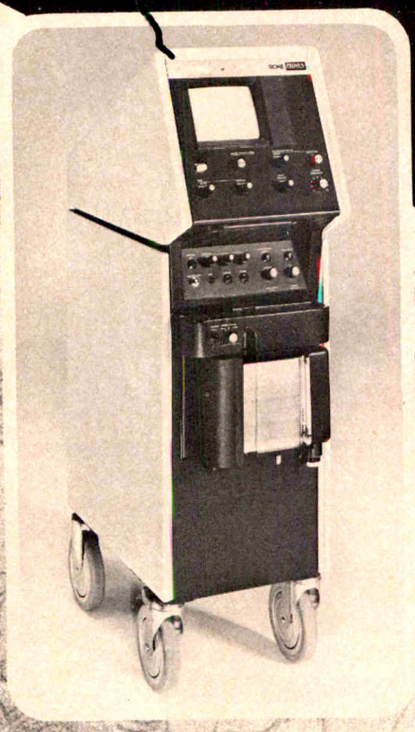

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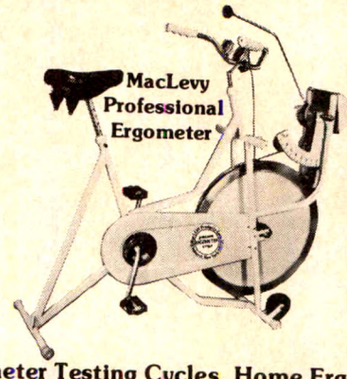

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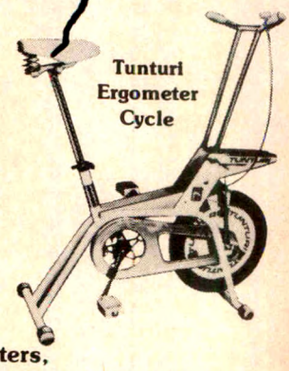

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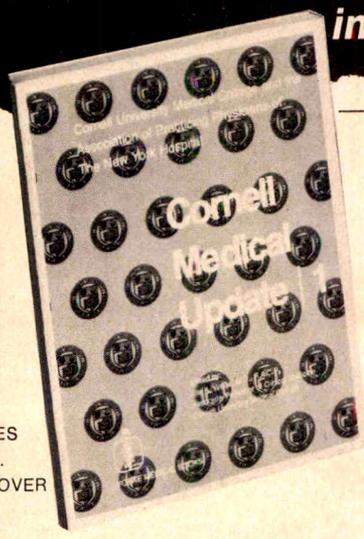

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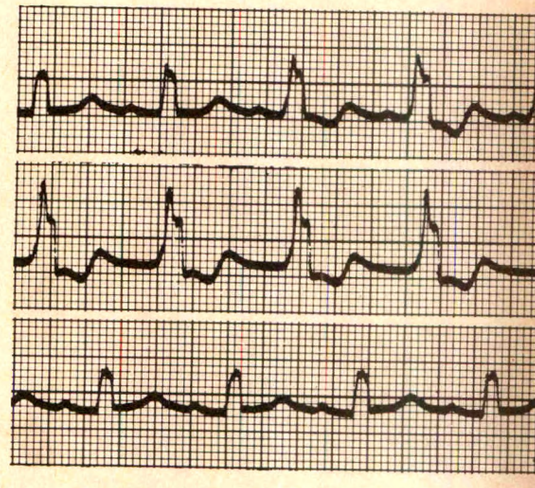

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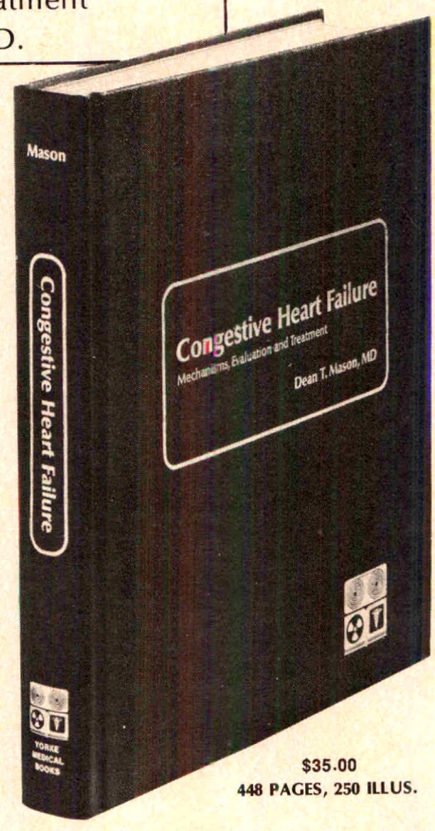

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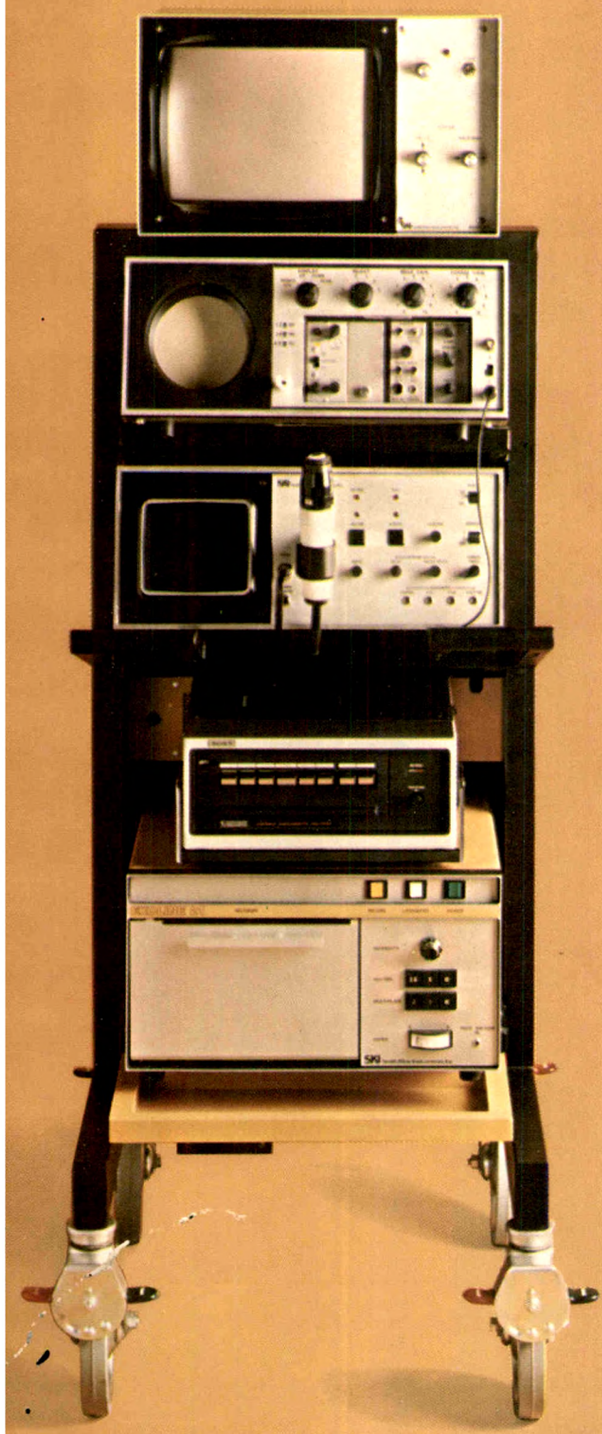

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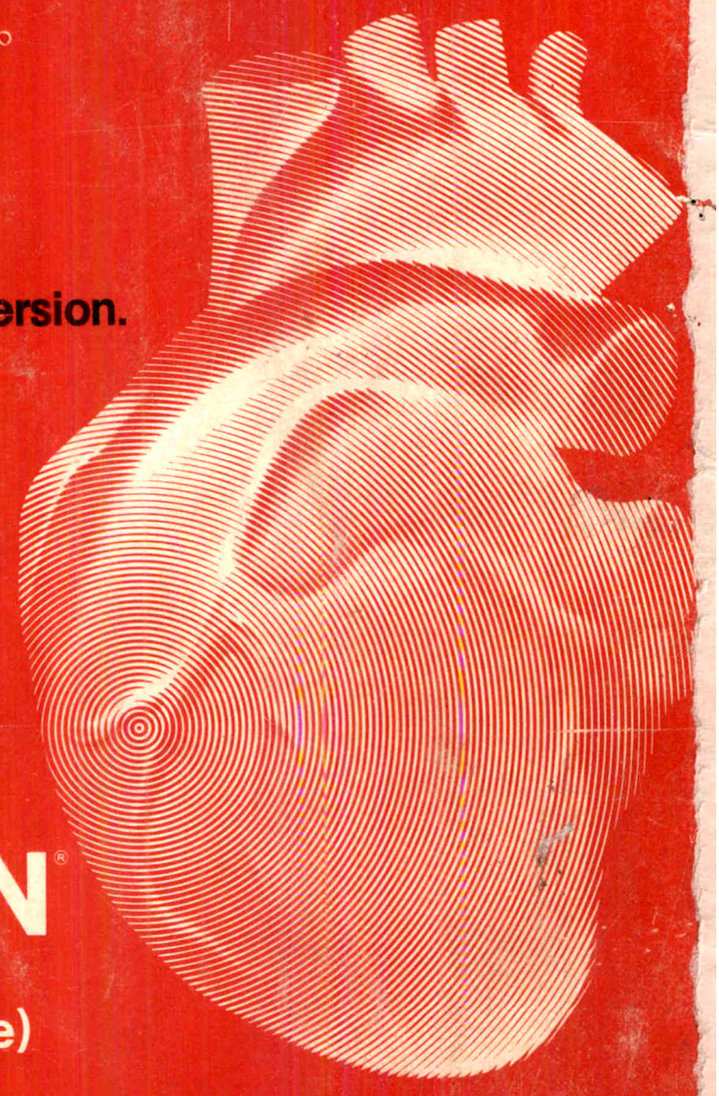

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